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The American Journal of Medicine

Vol. XV DECEMBER, 1953 No. 6

COLUMBIA-PRESBYTERIAN MEDICAL CENTER— 25th ANNIVERSARY

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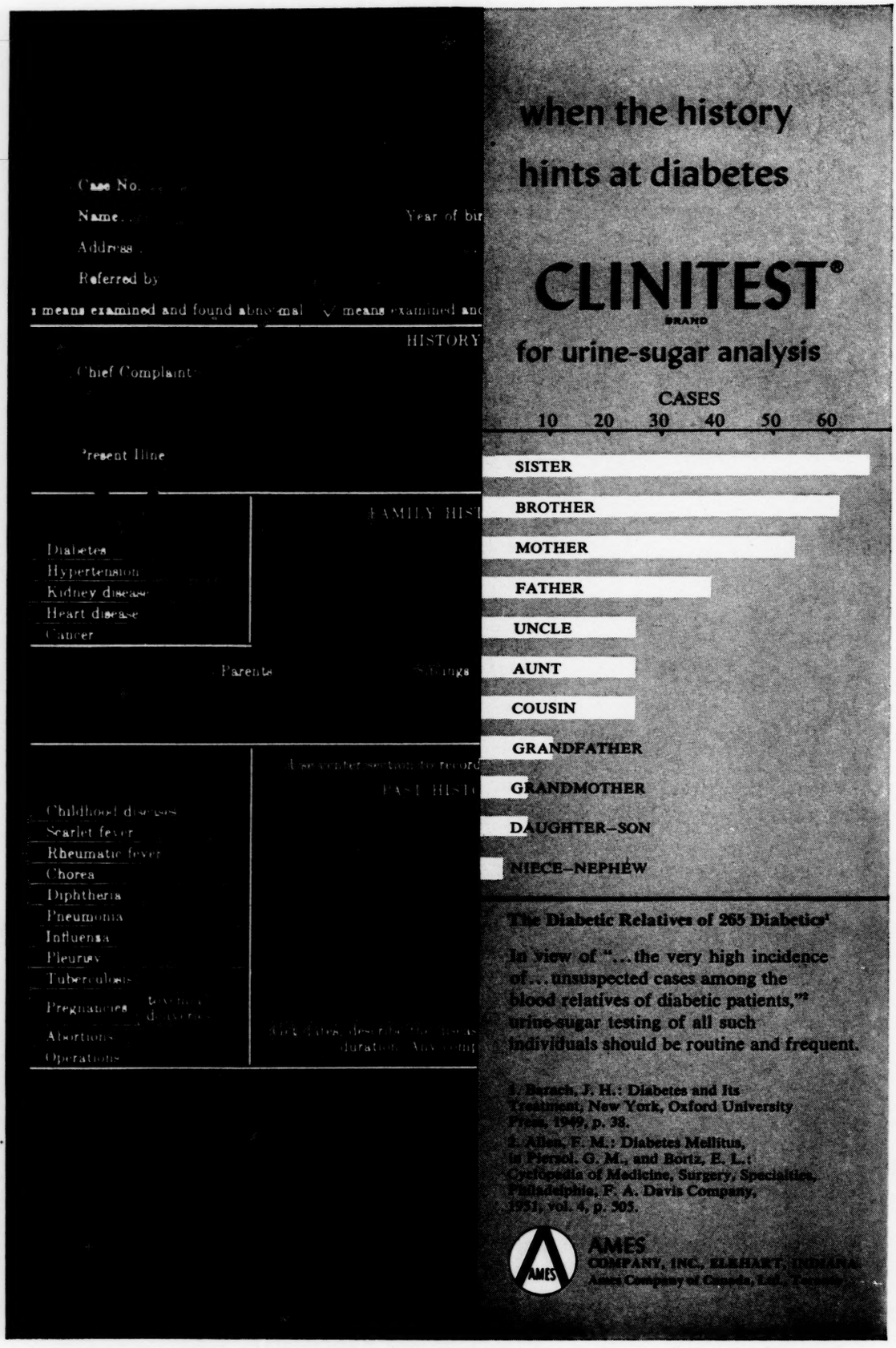

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1. Baruch, J. H.: Diabetes and Its Treatment, New York, Oxford University Press, 1949, p. 38.
2. Allen, F. M.: Diabetes Mellitus, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery, Specialties, Philadelphia, F. A. Davis Company, 1951, vol. 4, p. 505.

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Ames Company of Canada, Ltd., Toronto

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The American Journal of Medicine

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Combined Staff Clinic

Malabsorption Syndrome 790

Medical school and teaching hospital can be functionally integrated most satisfactorily by physical approximation, as Time has abundantly proved, and therein lies the significance of the evolution of the Medical Center concept in the development of medical education in this country. To mark the twenty-fifth anniversary of one such University-Hospital amalgamation, the Columbia-Presbyterian Medical Center, this issue of the American Journal of Medicine is dedicated. Dr. Willard C. Rappleye, Dean of the Columbia University College of Physicians and Surgeons, serves as Guest Editor and reviews the purpose and accomplishment of this great enterprise. Dr. Albert R. Lamb contributes a charmingly informal account of the early struggles in organization, touching upon the strong personalities who led the way. Then follows a condensed symposium on electrolyte metabolism by representative members of the Center. Finally, a Combined Staff Clinic is included to symbolize the union of basic and applied research to resolve the problems of the patient.

End of Medical Center Anniversary Symposium

Reviews

Coma Mechanisms . . . . . JOSEPH F. FAZEKAS AND ALICE N. BESSMAN 804

This is an informative discussion of coma mechanisms from an unusually basic point of view, that of the biochemist interested in cerebral metabolism and enzyme systems, and of the physiologist oriented toward problems relating to regulation of cerebral blood flow and gas exchange. The causes of coma are divided into four categories: substrate insufficiency, enzymatic disturbances, oxygen insufficiency and multiple etiologies, and are analyzed along these lines. The paper should give better insight into clinical management.

Toxic Psychoses and Allied States . . . . . SIDNEY COHEN 813

Delirium is an all too familiar problem in general medicine and one often not well understood or appropriately managed. In this excellent review Dr. Sidney Cohen deals with the diverse etiologies of the toxic psychoses, their diagnosis, prognosis, prophylaxis and treatment. His discussion is lucid and so applicable to the bedside that it will be particularly appreciated by the internist and student.

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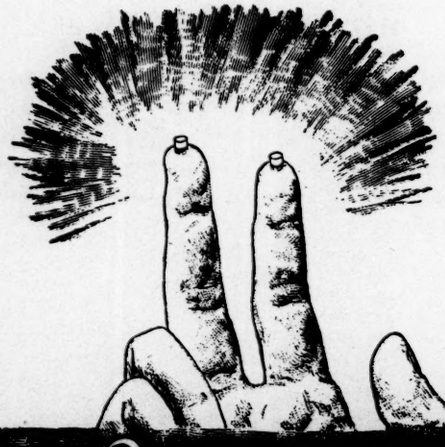

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Seminars on Neuromuscular Physiology

The Myopathies: Including Their Appearance in Constitutional Disease
K. L. ZIERLER AND J. L. LILIENTHAL, JR. 829

The authors first consider the "primary" myopathies, including the muscle dystrophies, myotonias, polymyositis, periodic paralysis and a variety of metabolic and miscellaneous disorders originating in muscle. This is followed by a discussion of abnormalities of the muscle secondary to disuse, endocrine diseases, environmental influences and infections. The whole affords excellent perspective in clinical evaluation of the disorders of the musculature.

Case Reports

A Simultaneous Study of Glycine-N^{15} Incorporation into Uric Acid and Heme, and of Fe^{59} Utilization, in a Case of Gout Associated with Polycythemia Secondary to Congenital Heart Disease
T'SAI FAN YÜ, LOUIS R. WASSERMAN, JEAN D. BENEDICT, EDWARD J. BIEN, ALEXANDER B. GUTMAN AND DEWITT STETTEN, JR. 845

Using glycine-N^{15} as tracer, overproduction of urate could be demonstrated in this case of gout complicating secondary polycythemia but peak incorporation of N^{15} into uric acid was much slower than in primary gout. This is related to the relatively slow turnover rate of red cell precursor nucleic acids, from which the excess urate was presumed to derive. Simultaneous heme-N^{15} and Fe^{59} utilization studies afforded independent measures of the increased erythropoiesis associated with the polycythemia.

Uric Acid Production in a Case of Myeloid Metaplasia Associated with Gouty Arthritis, Studied with N^{15}-Labeled Glycine
LEONARD LASTER AND ALEX F. MULLER 857

Glycine-N^{15} was fed to a patient with myeloid metaplasia who developed typical gout in the course of that disease and the rate of isotope incorporation into urinary uric acid was determined. The uric acid-N^{15} was found to increase slowly, with a peak at the fifteenth day, at which time the amount incorporated was twice normal. Evidence of excessive uric acid production, presumably the result of increased nucleic acid turnover, was thus obtained in this case.

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* *Non-Industrial Dermatoses of Allergenic Origin*
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Multiple Myeloma Simulating Hyperparathyroidism. A Clinical Pathologic Study
KENNETH E. COSGROVE AND KENNETH A. LATOURETTE 862

This interesting case, well studied and thoroughly discussed, crystallizes many interesting aspects of multiple myeloma.

Prostatic Fibrinolysin. Study of a Case Illustrating Role in Hemorrhagic Diathesis of Cancer of the Prostate
HENRY J. TAGNON, PHYLLIS SCHULMAN, WILLET F. WHITMORE AND LOUIS A. LEONE 875

The recent studies on prostatic fibrinolysin by this group of authors are of unusual interest because they help to explain the pronounced hemorrhagic tendencies in some patients with metastatic carcinoma of the prostate gland.

Hyperosmolarity of the Extracellular Fluid in Encephalitis . . . T. D. ULLMAN 885

This case, which the author considers to be one of encephalitis, illustrates the striking hyperosmolarity of the extracellular fluid which may be associated with brain lesions. A rational mechanism is proposed.

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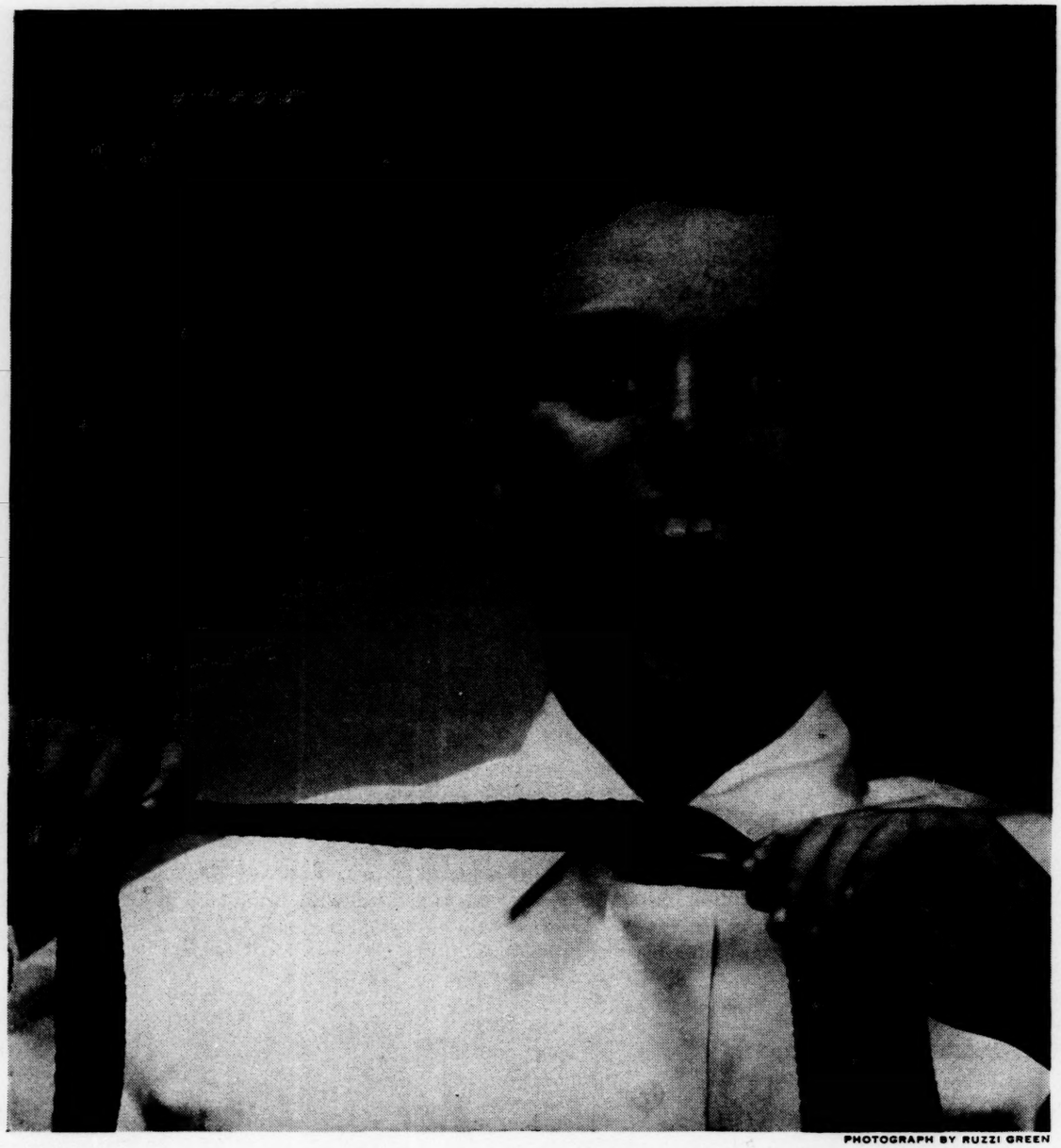
Change of address must reach us one month preceding month of issue.



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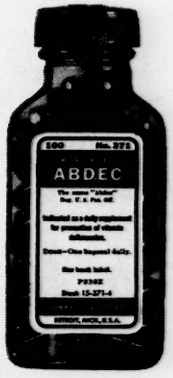

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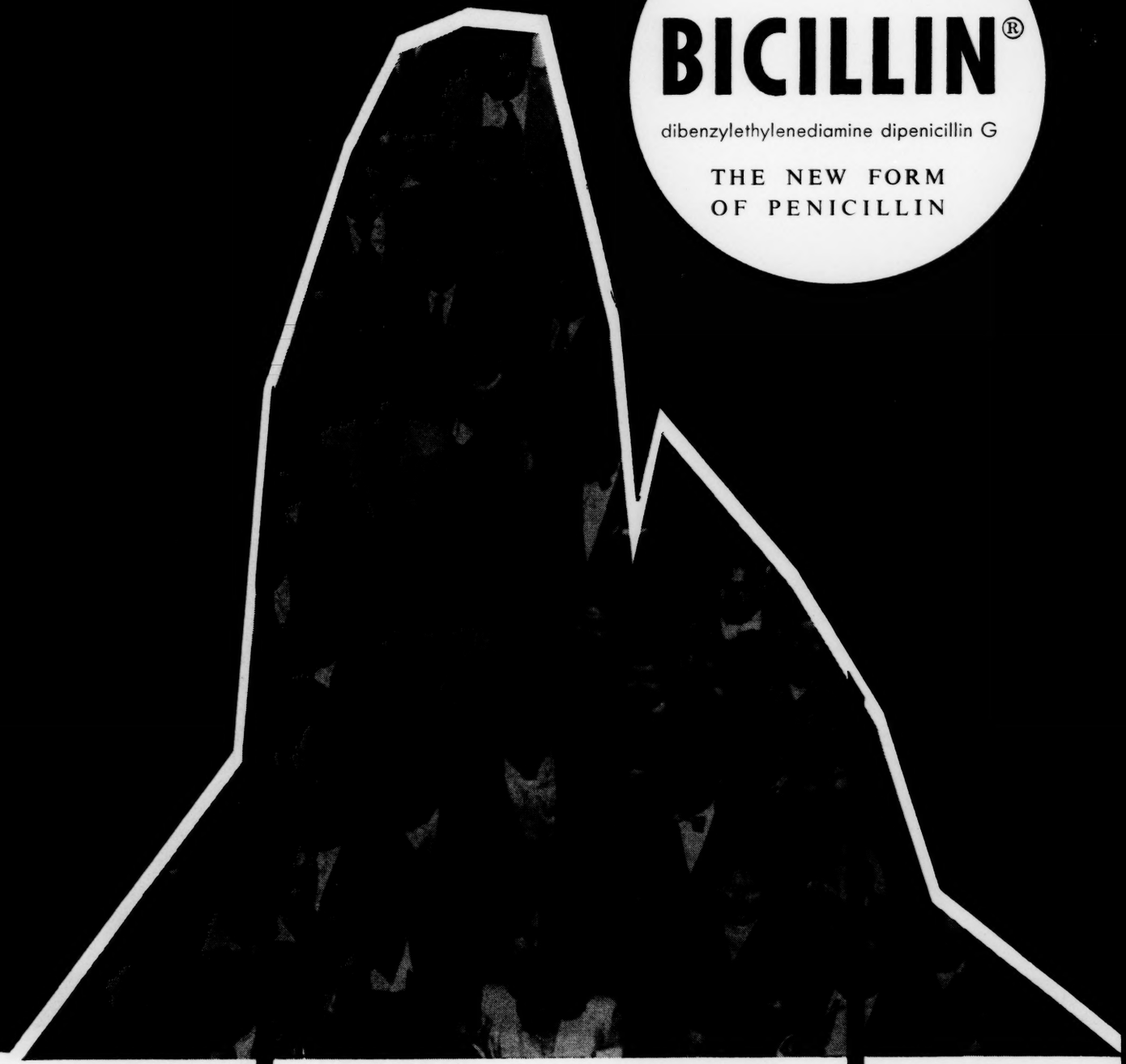

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Kountz, W. B.: Ann. Int. Med. *35*:1055, 1951.

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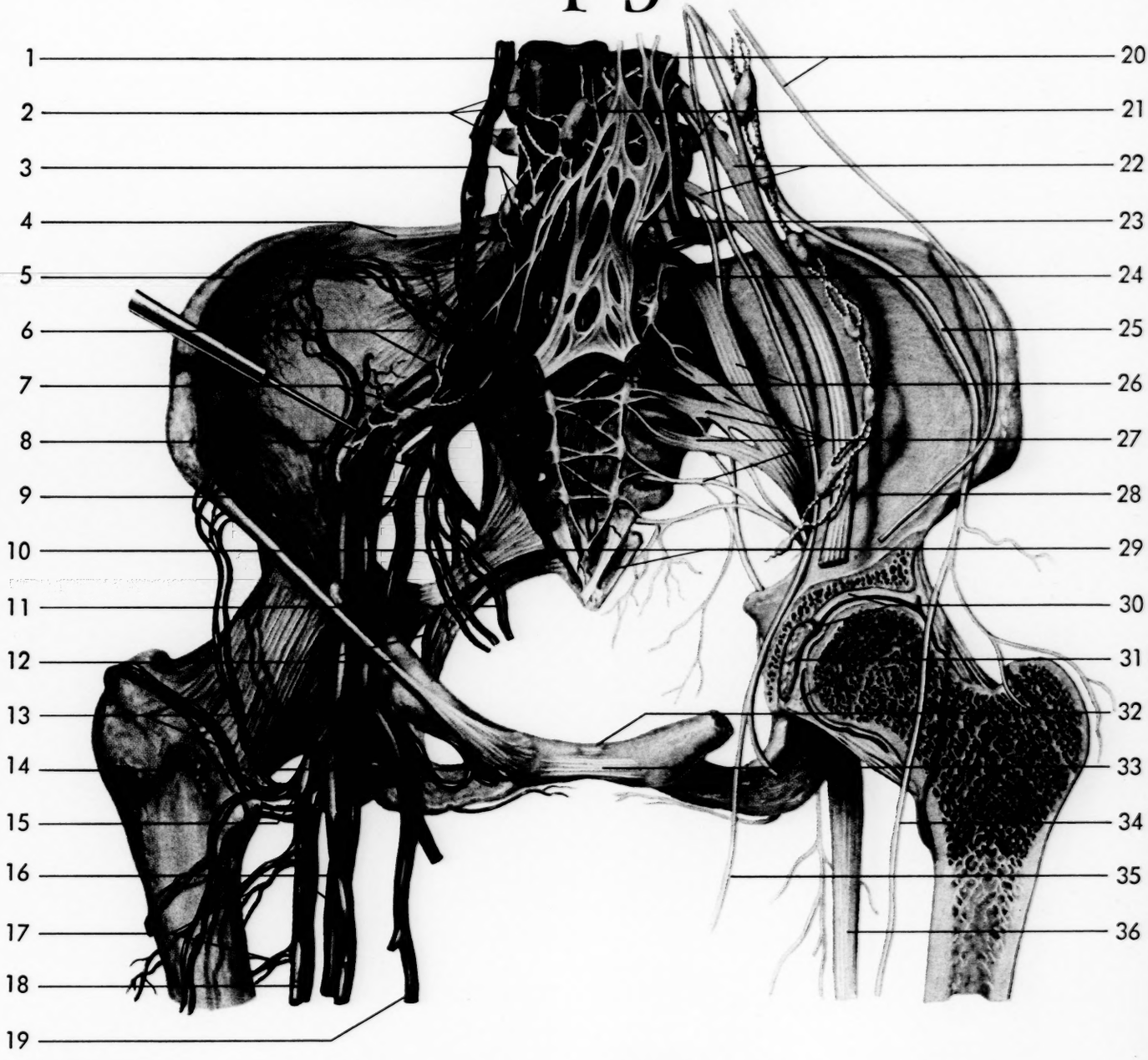
Anatomy *of the* Pelvis *and* Hip Joint



1 Ovarian artery and vein
2 Vena cava; lumbar lymph nodes
3 Right common iliac artery and vein
4 Iliolumbar ligament; branches of iliolumbar artery and vein
5 Lumbosacral ligament; superior gluteal artery and vein
6 Anterior sacroiliac ligament; internal iliac (hypogastric) artery
7 External iliac artery and vein
8 Obturator artery and vein
9 Inferior gluteal artery and vein
10 Sacrospinous ligament; uterine artery and vein
11 Sacrotuberous ligament; vaginal artery and vein
12 Inguinal ligament; internal pudendal artery
13 Iliofemoral ligament; branches of lateral femoral circumflex artery and vein
14 Lacunar ligament
15 Lateral femoral circumflex artery and vein
16 Femoral artery and vein
17 Perforating arteries and veins
18 Deep femoral artery and vein
19 Great saphenous vein
20 Aorta; ilioinguinal nerve
21 Lateral aortic lymph nodes
22 Lumbar nerves
23 Hypogastric sympathetic plexus
24 Sympathetic trunk
25 Lateral femoral cutaneous nerve
26 Middle sacral artery and vein; lumbosacral trunk
27 Sacral nerves
28 Femoral nerve
29 Lateral sacral artery and vein; anterior sacrococcygeal ligament
30 Lunate articular cartilage; joint cavity
31 Acetabular fat pad; ligamentum teres
32 Interpubic fibrocartilage
33 Superior pubic ligament
34 Anterior branch of lateral femoral cutaneous nerve
35 Obturator nerve
36 Great sciatic nerve

This is one of a series of paintings by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.

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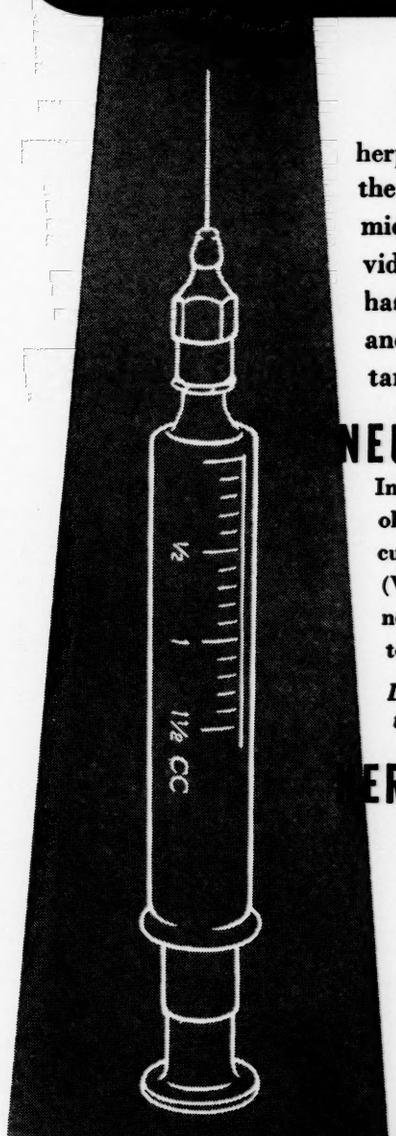

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Antibiotics & Chemotherapy *3*:299 (March) 1953.

Improvement in 113 of 124 Patients*

Diagnosis	Number of patients	Improved
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Chronic allergic rhinitis	26	25
Right maxillary sinusitis	2	1
Chronic naso-pharyngeal catarrh	6	6
Chronic suppurative sinusitis	3	3
Coryza, Head cold, Catarrhal rhinitis	58	51
Influenza	2	1
Acute catarrh	4	3
Hypertrophic rhinitis	12	12
TOTAL	124	113 (91.1%)

* Eye, Ear, Nose and Throat Monthly *32*:512 (Sept.) 1953.

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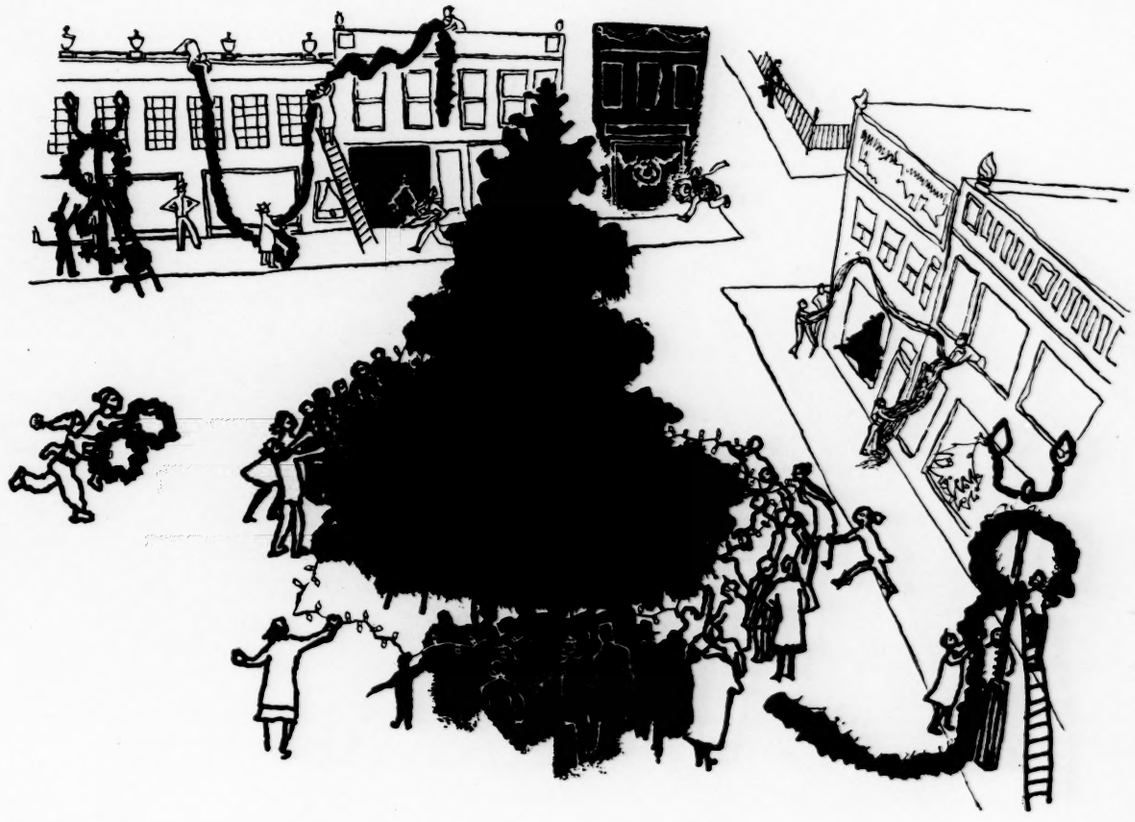

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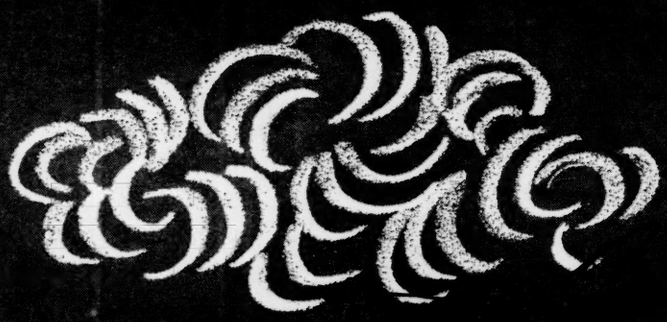

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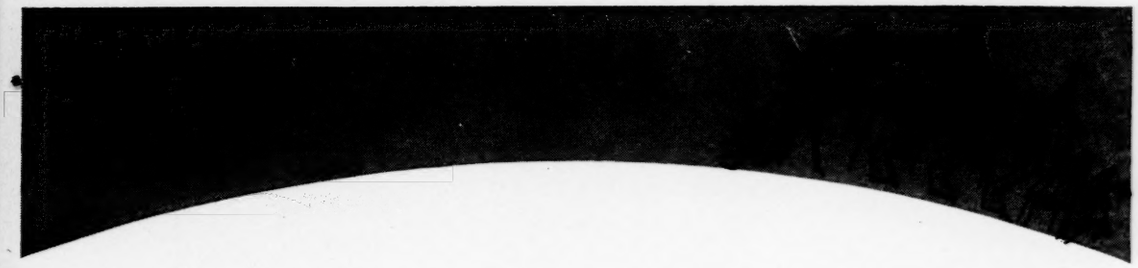

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Bibliography

(1) Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952. (2) Byron, C. M., and Orenstein, H. B.: New York State J. Med., *53*:676 (March 15) 1953. (3) Gutman, A. B.: Am. J. Med. *13*:744, 1952. (4) Rowe, A., Jr.; Tufft, R. W.; Mechanick, P. G., and Rowe, A. H.: Am. Pract. & Digest. in press. (5) Kidd, E. G.; Boyce, K. G., and Freyberg, R. H.: Prepared for publication. (6) Steinbrocker, O.; Berkowitz, S.; Ehrlich, M.; Elkind, M., and Carp, S.: J.A.M.A. *150*:1087 (Nov. 15) 1952. (7) Currie, J. P.: Lancet 2:15 (July 5) 1952. (8) Patterson, R. M.; Benson, J. F., and Schoenberg, P. L.: U. S. Armed Forces M. J. *4*:109, 1953. (9) Stephens, C. A. L., Jr.; Yeoman, E. E.; Holbrook, W. P.; Hill, D. F., and Goodin, W. L.: J.A.M.A. *150*:1084 (Nov. 15) 1952. (10) Smith, C. H., and Kunz, H. G.: J. M. Soc. New Jersey *49*:306, 1952. (11) Davies, H. R.; Barter, R. W.; Gee, A., and Hirson, C.: Brit. M. J. 2:1392 (Dec. 27) 1952. (12) Kuzell, W. C., and Schaffarzick, R. W.: California Med. *77*:319, 1952. (13) Granirer, L. W.: J.A.M.A. *150*:1332 (Nov. 29) 1952. (14) Steinbrocker, O.: J.A.M.A. *151*:143 (Jan. 10) 1953. (15) Hinz, C.; Lamont-Havers, R. W.; Cominsky, B., and Gaines, L. M.: J.A.M.A. *151*:38 (Jan. 3) 1953. (16) Stifel, J. L., and Burnheimer, J. C.: J.A.M.A. *151*:555 (Feb. 14) 1953. (17) Bershof, E., and Oxman, A. C.: J.A.M.A. *151*:557 (Feb. 14) 1953. (18) Burns, J. J.; Schulert, A.; Chenkin, T.; Goldman, A., and Brodie, B.: J. Pharmacol. & Exper. Therap. *106*:375, 1952. (19) Wilkinson, E. L., and Brown, H.: Am. J. M. Sc. *225*:153, 1953. (20) Domenjoz, R.: Internat. Rec. Med. & Gen. Pract. Clin. *165*:467, 1952. (21) Delfel, N. E., and Griffin, A. C.: Stanford M. Bull., in press.

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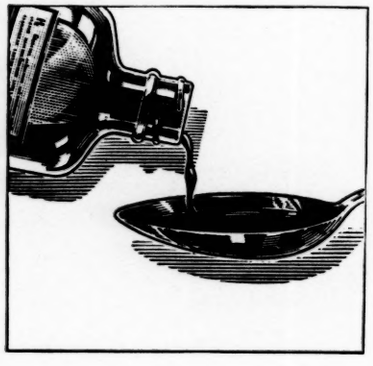

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**Annals of Internal Medicine*, 37:465, 1952.

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The American Journal of Medicine

VOL. XV DECEMBER, 1953 No. 6

Foreword

The Columbia-Presbyterian Medical Center

THE Columbia-Presbyterian Medical Center was conceived and built to integrate functionally and geographically the highest type of medical education, research and patient care. The feature that distinguishes it from the usual hospital and community medical service is the emphasis upon the education of physicians, nurses, dentists, public health officers, scientists, teachers and other professional personnel in the undergraduate, graduate and postgraduate fields and upon the advancement of knowledge in the medical sciences and its application in the clinical and social aspects of medicine. It is these very functions that insure the highest level of diagnosis, care and treatment of patients in the hospitals and clinics.

The affiliation of Columbia University with the Presbyterian Hospital and other institutions at the Medical Center, when it was put into effect twenty-five years ago, represented a fresh concept which attracted the generous support of farsighted benefactors. It paved the way for the signal advances which the Medical Center has made in the training of leaders of medical thought, in the technics and policies of medical education, in the store of knowledge of human biology and in services to the community and the nation.

The Medical Center is much more than the sum total of its individual units. The success of its program has depended upon and in the future will be determined primarily by the ideas and ideals which it represents and upon the men and the facilities that can be provided for them to attain these objectives of public service, education and research. It has endeavored to create an environment in which medicine of the highest scientific standards can be attained. The emphasis has been upon men and not upon bricks and mortar. The ideal of the Medical Center is to give further impetus to the development of medical knowledge which during the last fifty years has been more noteworthy than in the previous four thousand. Medicine today is on the threshold of unprecedented developments.

The leadership displayed by the Medical Center has exercised a wide influence. New centers, representing similar affiliations of hospitals with university medical schools, have been created in other parts of the country, as well as in New York City itself. The contributions of all of these groups have done much to bring American medicine to its present position of world leadership.

Perhaps it is well to recall the original remarks of President Nicholas Murray Butler at the ground-breaking of the Medical Center in 1925:

"The first turning of the soil on this spot is the beginning of the fulfillment of a prophecy that was made at the annual commencement of King's College held one hundred and fifty-six years ago. It is the beginning of the accomplishment of a dream that has been in the minds of many of us for a generation past. It signifies that at last the two aspects of medicine—the scientific and the philanthropic—are to be united in bonds that cannot be broken, as part of a new and vital union of organization, of purpose, and of public service. It means that a fully equipped university shall hereafter have at the service of its teachers in medicine an ample and thoroughly modern series of laboratories and clinics. It means that a noble hospital with a long record of public service behind it, from this day forth commands the best, the very best, that science, academic experience and personal devotion can give to ground the service of that hospital on the unshakable foundation of modern science in all its many-sided phases.

"Here on this site, through generous and broad-minded cooperation of many groups, and with the princely benefactions of those whose highest concern is for man, we propose to build

a monument more lasting than bronze which shall testify alike to the growing power of human knowledge to minister to the physical and mental ills of man and to the zeal of civilized man to help and to cure his less fortunate fellows."

On the same occasion, Mr. Dean Sage, President of the Board of Managers of Presbyterian Hospital, said:

"Many years ago two partners, Columbia University and the Presbyterian Hospital, conceived a vision. That vision was born of a wish to accomplish for the City of New York a broad union of the forces of Medical Practice, Education and Research, to the end that man might reap the benefit."

At the dedication of the Medical Center in 1928 President Butler again remarked:

"On the very day which marks the anniversary of the discovery of the new world by Christopher Columbus, it is becoming that Columbia University, a vigorous and eager child of that new world and its ardent spokesman, should mark with distinction and large acclaim the effective and noble completion of a great project of highest scientific importance and public interest, originally brought forward at the Commencement of King's College on May 16, 1769 by Dr. Samuel Bard, Professor of the Practice of Medicine in that early and foundling institution. So long has it taken for the wit and the capacity of men to realize in the field of practice the ideal which that forward-facing mind then saw in imagination and in prophecy!"

On this the twenty-fifth anniversary of the dedication of the Medical Center, we of the second generation applaud the wisdom, foresight and courage of the leaders of the preceding generation which made possible this pioneering endeavor which has meant so much to the people of the City of New York, to medical education and to the advancement in medical science and public health. The principles laid down in the original affiliation agreement of 1911 between the University and the Hospital, and subsequently reaffirmed in the agreement of 1921 under which the Medical Center continues to operate, emphasized the importance of the educational and research activities of the Center which, in turn, have guaranteed the maintenance of the highest quality of patient care in the hospitals and clinics of the joint enterprise.

The original agreement of 1911, and its successor of 1921, provided that the University should have the responsibility of nominating all the professional personnel on the hospital staff and that students should be admitted to its wards and facilities to provide instruction of future physicians, dentists, nurses and other health personnel. This could be fully accomplished only through a complete geographic integration of the laboratory, research, clinic and hospital facilities, in order that the newer scientific developments of the laboratories and research units could immediately be placed at the disposal of those studying the mechanisms and physiologic problems of illness, injury and disability in patients, all under the control and management of competent clinicians.

The extent to which the program has been realized can bring only deep satisfaction to those who made the Center possible. There are no indications or serious suggestions for changes in the policies adopted at the very beginning. The foundations have been laid securely for one of the great contributions to medicine in the future. The Medical Center must anticipate the health requirements of the next generation in order to continue its primary purpose of professional education, the advancement of knowledge and service to the public. These require a high order of imagination and foresight, sound leadership and courage in the formulation of educational and hospital planning.

The faculty and staff of the Medical Center have contributed materially to the sound evolution of medical education through the continued emphasis upon scientific medicine, that must remain the basis of medical practice and care in the future, to which is added the interpretation of social, psychologic, emotional and economic factors in the care, treatment and study of patients. The teaching programs of the University in the undergraduate, graduate and post-graduate training of physicians have never lost sight of the patient as the unit of medical care. Contributions to these broad concepts include the creation of the social service department, perhaps the first of its kind in this country. The follow-up clinics and the unit history system were established in recognition of the "longitudinal" study of patients as distinguished from the purely cross section method of observation, so common in teaching clinics elsewhere.

The study of stress as a factor in health and disease and the development of the "personality

panel" indicate the early recognition by the Faculty of these important concepts. The introduction of psychiatric teaching on all of the wards in the hospitals and in student clerkships points clearly to an endeavor to understand the total individual and the relationships between psychologic and emotional factors and their influence on bodily function.

Seven years ago the group clinic was established for the fourth year of teaching. After the first year, the medical course in effect operates throughout twelve months of the calendar year. The concept of group practice has made it possible to bring the highest type of integrated instruction to bear upon the actual care of patients. The Medical Center has taken active leadership in the study of chronic diseases both at the Center and through its affiliation with the Goldwater Memorial Hospital. The opportunities for experience in the highest type of rural practice at the Mary Imogene Bassett Hospital in Cooperstown and the instruction in industrial medicine, nursing procedures and public health are other illustrations of the broad base of the teaching program.

The philosophy in the educational program has been shifted from the earlier ideas of teaching by the faculty to learning by the student. This defines the medical course itself only as the foundation for the necessary continuous self-education of the successful physician throughout his professional career. The concept regards the four-year medical course as a unit, rather than a series of isolated subjects by integrating the basic sciences and clinical disciplines through correlation and combined clinics and other instructional devices. The program emphasizes instruction in group and rural medical practice, leadership in the fields of graduate and post-graduate medical education, new developments in administrative medicine, the role of the basic medical sciences in sound clinical teaching and practice, the importance of the chronic diseases, preventive medicine, psychiatry, psychosomatic medicine, the handling of emergencies, the development of the full-time system of university teaching and research and concentration at the Medical Center of a large proportion of the staff on the geographic full-time system, as illustrations.

Using the Medical Center as a base of operation the University has worked out numerous affiliations with other hospitals, health departments, industry, prepayment insurance plans, home care services and a wide variety of community activities designed to strengthen the health and professional services for the entire New York area. It has made noteworthy contributions in the continued education of physicians and in the residency training in a number of affiliated hospitals, and has constantly striven toward maintenance of high standards of medical practice in the country.

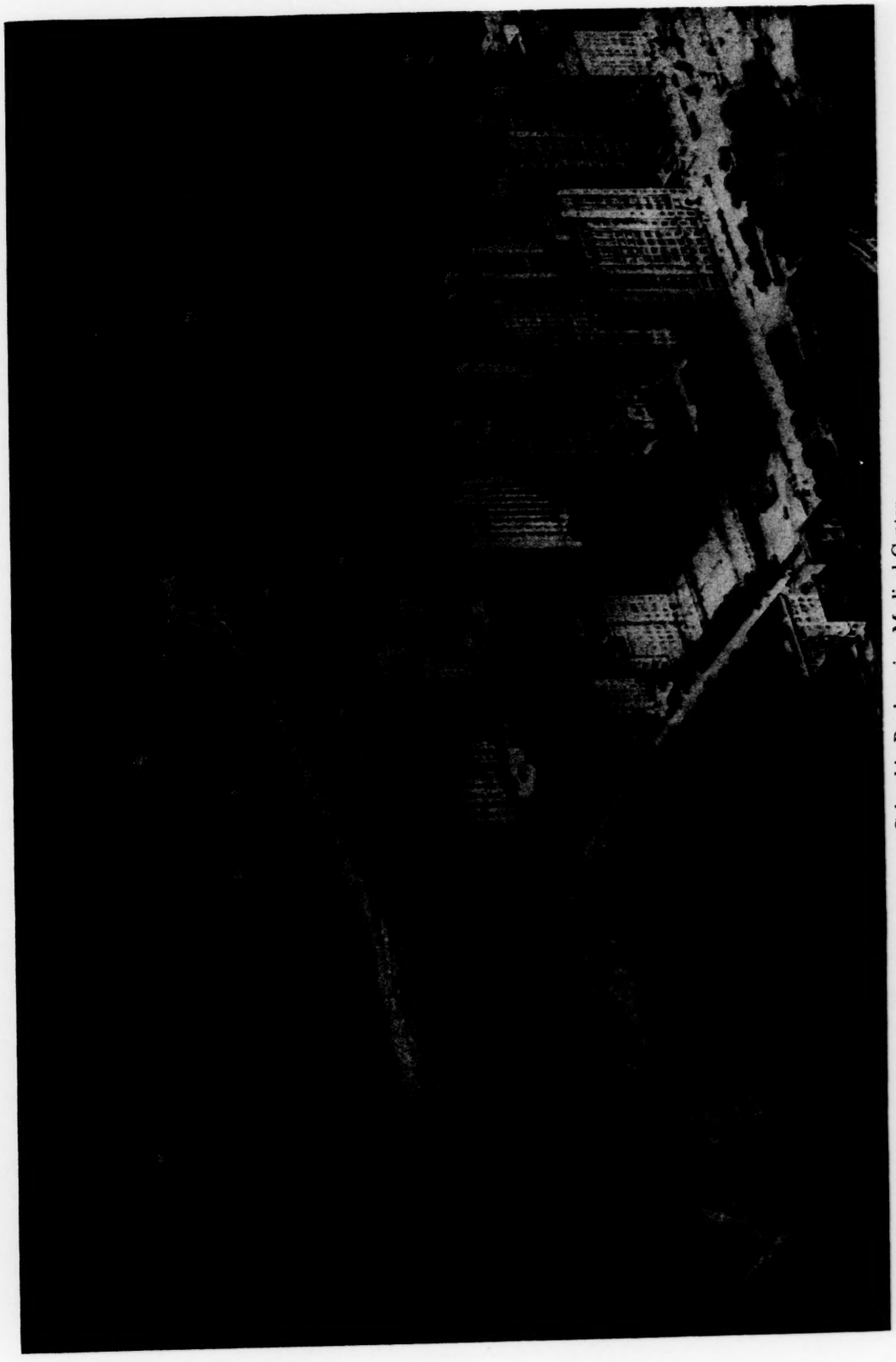
The impressive contributions to medical science can be well illustrated by a few examples, such as those on the pituitary gland and its hormonal interrelations, the pioneer studies of isotopes in intermediary metabolism of a variety of physiologic substances, the discovery of the structural formula of vitamin B_1, the development of quantitative immunochemistry, experimental studies of muscular dystrophies, the chemistry of blood group substances and the role of blood volume in shock, the portacaval shunt in the treatment of cirrhosis of the liver and other advances in cardiac and blood vessel surgery, successful resection of the head of the pancreas for cancer, discovery of bacitracin, studies in the diagnosis and treatment of adrenal tumors, iodine uptake in thyroid carcinoma, definition of electrolyte disturbances in Addison's disease, the role of streptococcal infection in scarlet fever and rheumatic fever, the dietary treatment of cirrhosis of the liver, the physiology of heart disorders and the introduction of cardiac catheterization, demonstration of viral etiology of the common cold, first clinical use of penicillin in the United States, the cephalin flocculation reaction, discovery of acid phosphatase in the blood and its use in the diagnosis of cancer of the prostate, the first clinical use of vitamin B_{12}, introduction of helium-oxygen mixtures for obstructed breathing, serologic methods for the diagnosis of rheumatoid arthritis, chemical recognition of pheochromocytoma and the role of nor-epinephrine, contributions in electrophoresis, the chemistry of the cell nucleus, the isolation of the milk factor in breast cancer in mice, pioneer studies of circulation with radioactive sodium, the measurement of radiation dosages, research in the understanding and control of bleeding, advances in anesthesiology, the control of influenza meningitis and the character and behavior of bacterial genes.

Fully aware of the many and diverse responsibilities which revolve about the health services in the community and the nation which the several professions must carry, the University

can, in the long run, render its most important and broadest public service through the maintenance of a high level of professional education in the health sciences. It can and should carry its share of the obligation for hospital services, the continued education of practitioners and the preparation of specialists. Its greatest contribution, however, is to educate men and women to meet these responsibilities rather than to assume direct management of community services, except those necessary to discharge its function in society.

It is with high courage and confidence that the Medical Center accepts the challenge of the future and looks forward to the contributions which it can be expected to make during the period ahead, in the full realization that one of the greatest assets of any nation is the health of its people. In the final analysis the teaching institutions are the guardians of the health of the nation since the quality of medical education and research ultimately determines the standards of medical care. To the improvement and betterment of that great national asset, the Medical Center on its twenty-fifth anniversary re-dedicates itself with full vigor and confidence.

WILLARD C. RAPPLEYE, M.D.
Dean, Faculty of Medicine,
Columbia University



Columbia-Presbyterian Medical Center.

The Story of the Founding of the Columbia-Presbyterian Medical Center

ALBERT R. LAMB, M.D.

New York, New York

How did there happen to be a Columbia-Presbyterian Medical Center? The answer is fairly simple. The trigger mechanism was the question of allowing medical students to work on the wards of a hospital—clinical clerks as we now know them. The motivating force which this set off was the vision and the munificent and discriminating generosity of Edward Stephen Harkness. And this is not intended to detract one iota from the important roles played by the many able men and women who contributed without stint to the ultimate achievement.

The institutions thus brought closer together for the common good each had had an eventful history of which, however, only sufficient can be related here to furnish some background for the events leading up to the establishment of the Medical Center. Columbia University was founded as King's College in 1754, by royal grant of George II. In 1767 King's College organized a medical faculty, the second such in the Colonies and the first to confer the degree of Doctor of Medicine in course. Instruction in medicine continued until interruption by the Revolution, then was resumed in 1792. In 1814 the medical faculty of Columbia College was merged with that of the College of Physicians and Surgeons, chartered in 1807. In 1860 the College of Physicians and Surgeons became the Medical Department of Columbia College and in 1891 was formally incorporated as an integral part of the University. Stages in this development are illustrated in Figures 1 and 2, the latter representing the College of Physicians and Surgeons at the time the events to be described transpired.

The initial location and possibly the very existence of the Presbyterian Hospital were determined by an event which occurred in the first quarter of the last century. Mr. Robert Lenox, one of the foremost merchants of his day, purchased at public auction the "Five Mile Post Farm," comprising the land within the boundaries of what are now 68th and 71st Streets and Park and Fifth Avenues. He paid $6,420 for this piece of land, a price he considered to be grossly exorbitant. This land, together with an equal area between 71st and 74th Streets purchased shortly thereafter, was then known as "The Lenox Farm." Upon his death in 1839 Robert Lenox, still sure the property was not worth what he had paid for it, left it to his son James, expressing a wish, which was not binding, for him not to sell it as it might some day be the "site of a village." It would be interesting to know what "The Lenox Farm" would be worth today! We do know that the one block occupied by the Presbyterian Hospital, together with the small parcel for Nightingale Hall on 71st Street, was sold for $4,500,000 at the time of moving to its present site. No, Robert Lenox was not cheated!

By 1864 James Lenox began to dispose of various parcels in charitable gifts for the Lenox Library, The Home for Aged Women and the Phillips Presbyterian Church. On January 2, 1868, he wrote to thirty-two prominent citizens of New York inviting them to join as Managers in establishing a Presbyterian Hospital in the city. So carefully had everything been prepared that progress was rapid and James Lenox donated the block of land bounded by what are now Madison and Park Avenues and 70th and 71st Streets for the project, together with $100,000 to which sum he added liberally later on. On October 10, 1872, the Hospital was formally dedicated. It was considered the last word in hospital construction and equipment.

James Lenox, declining the use of his own name, introduced the Hospital to the world with the memorable words:

"The Presbyterian Hospital; Presbyterian in its burdens because founded by Presbyterians;

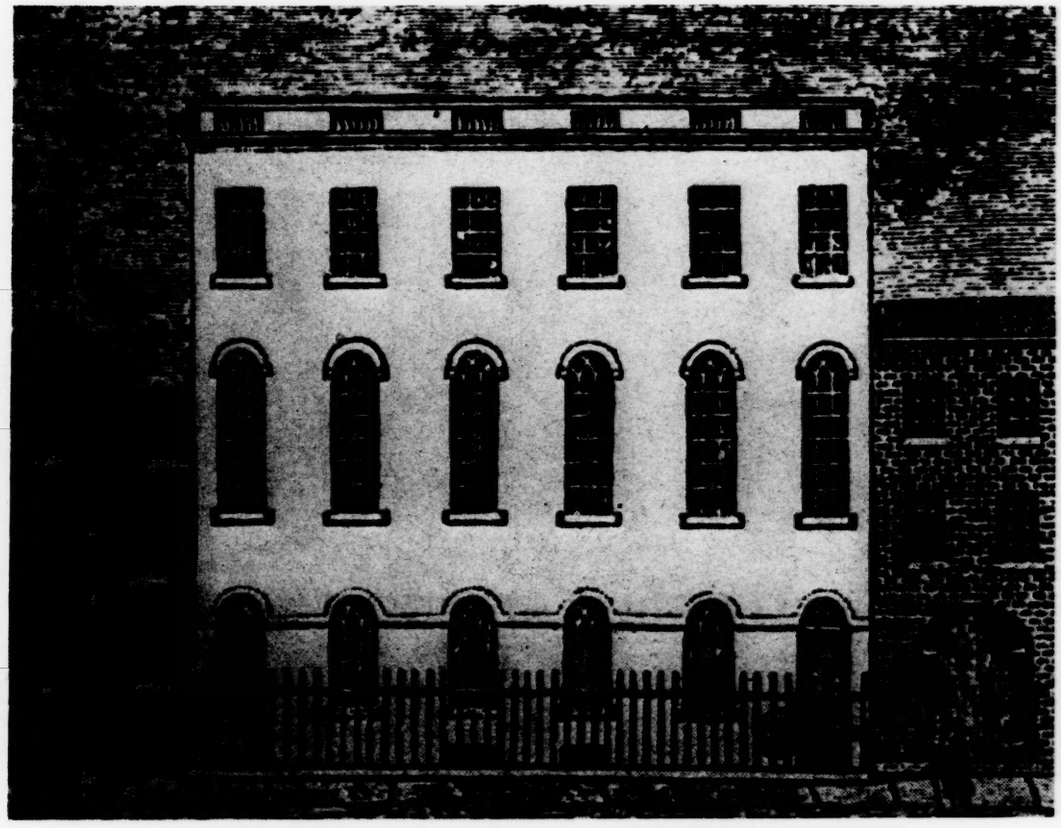


FIG. 1. College of Physicians and Surgeons at 3 Barclay Street (1813–1837).

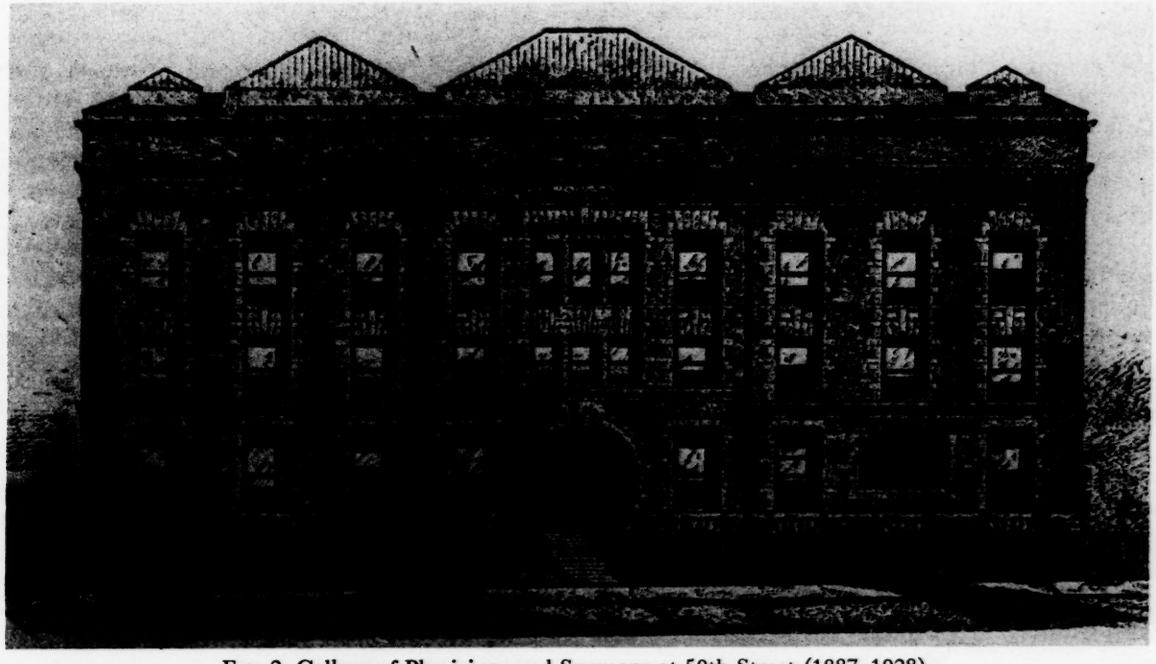


FIG. 2. College of Physicians and Surgeons at 59th Street (1887–1928).

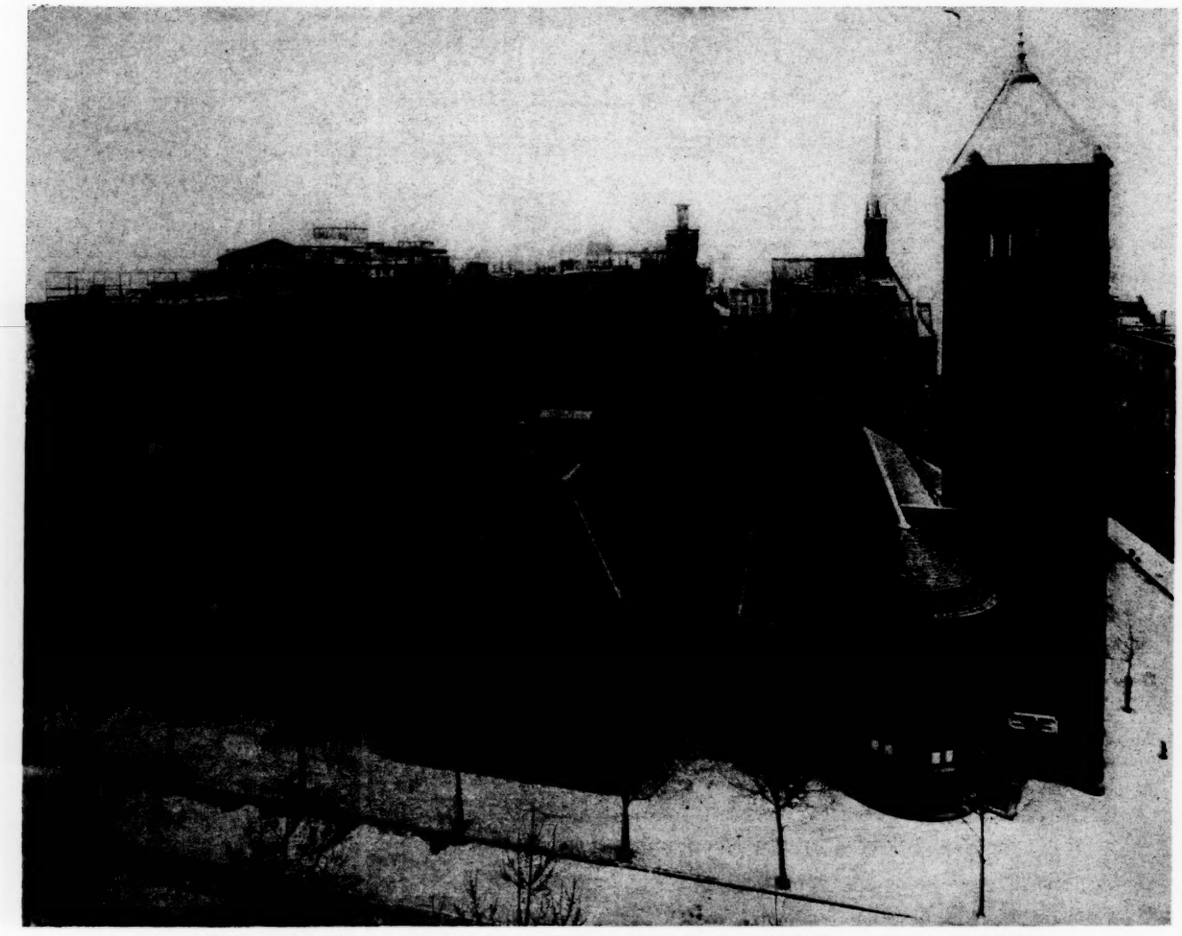


FIG. 3. The old Presbyterian Hospital, Madison Avenue and 70th Street (May 28, 1910).

undenominational in its benefits because for the reception of patients irrespective of creed, nationality or color."

On the evening of December 19, 1889, the main Hospital Building was destroyed by a disastrous fire which fortunately spared the recently constructed Dispensary and Chapel Buildings which were used for the two years of reconstruction. The appearance of the Presbyterian Hospital at the time of the negotiations leading to the founding of the Medical Center is shown in Figure 3.

During the first decade of this century there was increasing realization by the leading medical schools of the country of the necessity for their students to obtain more direct contact with patients on the wards of a hospital. With this end in view the College of Physicians and Surgeons of Columbia had been negotiating with Roosevelt Hospital, their neighbors just across the street. Mr. Harkness, who was on the Roosevelt Hospital Board of Trustees at the time, generously offered to build and equip a surgical pavilion of 150 beds, a complete research laboratory, and to provide an endowment of $1,300,000 the income of which was to be used exclusively for scientific work, all predicated upon allowing the medical students at the College of Physicians and Surgeons to work on the wards and in the laboratories. Professional appointments in the hospital were to come through nomination by the University.

Mr. Harkness' offer was courteously rejected by the Roosevelt Hospital Board by a close vote. Mr. Harkness resigned from the Roosevelt Board and on December 13, 1910, was elected to the Board of Managers of the Presbyterian Hospital. Six days later he made to the Presbyterian Hospital an offer identical with that previously made to Roosevelt Hospital. This offer was accepted and on April 28, 1911, the first affiliation agreement between Columbia Uni-

versity and the Presbyterian Hospital was consummated.

Some years later, I remarked to Mr. Harkness that possibly there should be a statue of a clinical clerk on the grounds at the Medical Center. He replied, laughingly, that he guessed that was so.

With this affiliation of 1911 a great project had its birth. But it was to be seventeen years before the Medical Center was ready to operate, years in which many difficult problems had to be faced and solved and in which, at times, differences of opinion arose, some threatening the whole undertaking.

The first problem was the choice of a site, five of which were considered. On October 18, 1908, the President of the Presbyterian Hospital, Mr. John S. Kennedy, presented the Hospital with a gift of one million dollars in celebration of his golden wedding anniversary. This was to be used for construction purposes, more especially for a fireproof administration building. At his request the Medical Board, headed by Dr. Andrew J. McCosh, drafted a succinct report recommending the removal of the Hospital to "a larger and more adaptable plot of ground." That practically settled the fate of site number one at 70th Street and Park Avenue.

Site number two was a block along the East River, immediately south of where the New York Hospital now stands. Dr. McCosh, who was the dominant professional force at the Hospital, recommended this location. Mr. Kennedy bought this property for $500,000 on February 9, 1909, soon after the tragic death of Dr. McCosh, caused by his span of horses running away. He had scorned the new-fangled automobile.

A group of the leaders at the Hospital in the professional, administrative and nursing fields, after painstaking investigations of the site at various hours of the day and night, reported in May, 1909, against building the new Hospital on that site. And yet, strangely enough, essentially the same group less than five months later recommended that the new Hospital should be built there. In consequence of this later report the Managers authorized the preparation of sketch plans and the purchase of adjacent land for a Nurses' Residence. The plans contemplated an increase of private beds to forty!

Such was the situation when Ed Harkness joined the Board of Managers and was made Chairman of the Building Committee. Early in 1915 he reported for this committee that it was questionable whether the College of Physicians and Surgeons would move there and that there was also some question of its desirability from the Hospital's standpoint. His real reason was his firm belief in the need of space and room for expansion which the new site did not provide.

He had visited the large plot of ground at 168th Street and Broadway then used by the New York Highlanders Baseball Club, the forerunners of the New York Yankees, and was deeply impressed. On March 31, 1915, he reported for the Building Committee that this was the best site obtainable and that he, personally, had taken an option on the property for $2,000 and a down payment of $75,000 on the purchase price, assuming that Columbia University would raise the money to pay its share of buying the property, which I believe was priced at $1,500,000. This was the third site and the one eventually agreed upon, but not without long and sometimes discouraging negotiations.

During the summer of 1915 there were further discussions between Mr. Harkness and President Butler of Columbia University, the upshot of which was that Columbia could not raise its share of the property's purchase price or its share of the option renewals. Consequently, after renewing the option several times, the Hospital voted on November 20th to allow it to lapse. This seemed to end the matter insofar as the Washington Heights property was concerned. But anyone who knew Ed Harkness realized that once he had decided on a given course of action it was next to impossible to get him to deviate from it. He once told me that as a young man he had great difficulty in making up his mind. Realizing this he schooled himself not only to make decisions but also to stick to them once made.

The fourth site was the block at 116th Street and Amsterdam Avenue. This land had been donated to Columbia University for its Medical School. At one time an affiliation with St. Luke's Hospital and the College of Physicians and Surgeons on this site was considered. But nothing came of it or of having the Presbyterian Hospital move there.

The last site was the property, owned by Columbia University, on Gun Hill Road just north of the Bronx Reservoir and south of Woodlawn Cemetery. The Columbia War Hospital was built there. At one time during the negotiations Presbyterian Hospital agreed tem-

porarily to move to this site but nothing came of this.

There was one other move in these negotiations of much interest although now not generally known. That was a proposed merger of the New York and Presbyterian Hospitals and the Cornell and Columbia Medical Schools. However, nothing came of it as Columbia University believed that there were "insuperable legal obstacles" against it. In the meantime the affiliation agreement of 1911 was still in effect and working as well as it could with the Hospital and College not geographically united.

The leadership in the professional group of the Presbyterian Hospital devolved upon Dr. Joseph A. Blake, who had succeeded Dr. McCosh as head of the Surgical Service and who was entirely in favor of a University Hospital. Dr. Theodore C. Janeway, equally enthusiastic about the new ideas, headed the Department of Medicine and Dr. William S. MacCallum, a staunch advocate of University medicine, became Director of the Pathological Department. Dr. Warfield T. Longcope joined Dr. Janeway as his right hand man.

With the then major clinical departments well staffed, success seemed assured but resignations, war and other difficulties delayed achievement of the desired goal for a long time. Indeed, often it seemed that such a happy outcome never would be reached. First came the resignation of Dr. Blake in October, 1913. Four months later Dr. George E. Brewer was selected to fill his place. He had just enough time to organize the Surgical Department along sound lines before he became more and more engrossed in planning all of the details of the Presbyterian Base Hospital with which he went overseas as Surgical Director. He never returned to active service at Presbyterian Hospital, being succeeded by Dr. Adrian Lambert who served until 1921 when Dr. Allen O. Whipple took over, under the new affiliation agreement with Columbia.

There were parallel changes in Medicine. Dr. Janeway resigned in April, 1914, to head the Medical Department at Johns Hopkins Hospital on a strictly full-time basis and was succeeded by Dr. Longcope.

Upon the death of Dr. Janeway in 1917, Dr. Longcope took his place in the Surgeon General's office for a time and then went overseas as Medical Consultant in the A.E.F. for the duration of the war, Dr. Walter W. Palmer serving as Acting Director in Medicine. Dr. Longcope returned on the cessation of hostilities and Dr. Palmer went to Johns Hopkins Hospital. Upon the resignation of Dr. Longcope in 1921, Dr. Palmer became Medical Director, Dr. Longcope going to Johns Hopkins as head of the Medical Service there.

Mr. John S. Kennedy, President of the Hospital for a longer period than any other of our Presidents, and still a forceful and dominant figure in our affairs in spite of his seventy-nine years, had died of whooping cough in October, 1909. He was followed by Mr. Frederick Sturges who resigned in 1916, the only one of our Presidents to take such a step. As President Emeritus he died the following year. Mr. William Sloane was the next President. He served for the next six years during the period of trying controversies, war and two devastating "flu" epidemics but long enough to see the final affiliation agreement with Columbia University an accomplished fact.

It remained for Mr. Dean Sage, who succeeded Mr. Sloane on November 14, 1922, to bring together the various units comprising the Medical Center into a geographical union replacing the former paper affiliation, and to help guide the Medical Center in successful operation for nearly fifteen years until his death in 1943.

With such numerous and upsetting changes it is small wonder that it was next to impossible to carry out any clear-cut course of action. Negotiations, however, were continuing between committees from Columbia and Presbyterian.

The year 1919 brought significant changes. Early in the year the Dean of the College of Physicians and Surgeons, Samuel W. Lambert, retired; he had been one of the staunchest advocates of the hospital-medical school affiliation and had fought for it unremittingly. On July 1, 1919, Dr. William Darrach became Dean. No happier choice could have been made to meet the existing situation. He had a wide acquaintance among all medical groups, was a Yale classmate and a close friend of Ed Harkness, was tactful, forceful, respected and trusted by everyone.

On December 13, 1919 Dr. Darrach's noteworthy "Memorandum on the School of Medicine" appeared with the approval of the Committee on Administration. This described the several types of full-time system and advocated the complete form for the major departments.

The plan was so agreeable, not only to the Presbyterian Hospital and Columbia University but also to the Rockefeller Foundation, the General Education Board and the Carnegie Foundation, that a new affiliation agreement between Columbia and Presbyterian Hospital was executed February 10, 1921, operative on May 16th when Columbia was assured of gifts of one million dollars from each of the three Foundations. And Mr. Harkness and his mother gave the land, some twenty-two acres, at 168th Street and Broadway, one-half to Presbyterian and one-half to Columbia, the deed dated September 29, 1922.

The middle of 1921 saw the undertaking off to a most promising start. A five man staff, headed by Dr. Whipple, was to carry on the Surgical Service with Dr. Hugh Auchincloss heading the Second Division the year around and Dr. Fordyce B. St. John the First Division. They had decided to abide strictly by the letter of the law in the Dean's Memorandum. This did not mean, however, that they were fully in accord with some of its provisions. In Medicine, Dr. Palmer never tried to conduct the service along quite such strict lines, as he believed in flexibility. It did not take very long to find out that there were definite flaws in the plan.

Hearing the growing dissatisfaction Mr. Harkness had a dinner at his house on January 17, 1922, for a group of the most influential men on the staff to discuss the matter. As a result of the evening's discussion one definite improvement emerged, in addition to a better understanding of the whole situation by all concerned, although Mr. Harkness was reluctant to see any changes made in a plan already agreed to.

In 1921 Miss Anna Maxwell resigned as Director of Nursing. She had built up an outstanding School of Nursing since 1892 and had played a dominant role in all hospital affairs. Her successor, Miss Helen Young, first as Acting Director and then as Director, did a superb job in the transformation of the Hospital from a small family affair into a huge undertaking without losing any of the rare qualities which had made its reputation.

In 1923 the Committee on Organization of the Clinical Departments brought in a long report recommending that the Clinical Departments be organized along the same lines as all other Departments in the Medical School and College. This recommendation was made effective by the proper authorities as of January 1, 1924. It meant, according to the University Statutes, that any person could do extra-curricular work and receive compensation therefor so long as such work did not interfere with the interests of the University. The plan was misunderstood in certain sources and in some public statements because it had not been made clear that the full-time system had not been abandoned but merely modified to make it more workable. It was at this point that Dr. Palmer persuaded the two Rockefeller Boards (The Carnegie Foundation had never indicated its intention of cancelling its donation) that the full-time system was not being abandoned but merely altered in some particulars which were objectionable. Again, it was clear sailing and continued so insofar as any major obstacles were concerned.

Planning for the new Hospital and Medical School had gone ahead, not unduly disturbed by the foregoing events. Mr. James Gamble Rogers was selected as architect and Marc Eidlitz and Son as builders. Dr. C. C. Burlingame was appointed Executive Officer of the Joint Administrative Board late in 1921 when he was but thirty-six years old. Upon these comparatively young shoulders was placed much of the heavy burden of organizing the plans for the Columbia-Presbyterian Medical Center. Dr. Burlingame was one of those always ready "to greet the unknown with a cheer"—and to endeavor to improve upon it. He had had a considerable experience with hospital affairs both in civilian life and in his distinguished army service overseas during the war. His was an ebullient personality, hard working, hard driving and generally enough ahead of the times to be impractical.

The early phases of the planning were quite visionary—castles in the air. The cost was talked of lightly—perhaps fifty million dollars—and the buildings were to be anywhere from thirty to fifty stories tall. Hydroplane ambulances were to land in the adjacent Hudson River and airplane ambulances were to land on the roofs. But, as it turned out, the Medical Center has never had its own ambulance service.

Thirty-two stories were planned for Vanderbilt Clinic including eight floors for dentistry. Yet when the chips were down, later on, there was only enough money to build a story and one-half. It was only through the generosity of

Mr. Harkness and the Vanderbilts that an adequate building of eight stories was made possible. It was not until it was decided to limit the buildings to the size necessary to care adequately for the College's classes of 100 men that real progress began to be made and then it was made rapidly.

Early in 1923 one of those things happened which turned out to be of great value to the whole plan. Mr. John F. Bush, of Rochester, New York, stopped in to see his friend, Dean Sage. The two had been friends and had had dealings together. Mr. Bush had had wide experience in business, both in the operative and construction ends, but had been ill for a couple of years and was only just getting well enough to want to do something which was not too strenuous. Little did he realize at the time what he was heading into! Dean Sage was full of the new Medical Center plan and dwelt on it at length, ending up by asking John Bush if he would like to join the project since the Superintendant, Dr. Young, was leaving. Surprised, Mr. Bush said: "Why, Dean, what do I know about hospitals? I was never even in one but once when I had an accident." To which Mr. Sage replied: "Well, for that matter, John, what do I know about them." They were both to know plenty about hospitals before their careers were over.

Mr. Bush took over as Superintendent on April 1, 1923, and not long thereafter as Executive Vice-President, replacing Dr. Burlingame who had his hands full with the Joint Board. Dean Sage and John Bush worked together for a good many years and formed a well rounded team as each could do certain things easily which the other could do only with difficulty.

It would be neglectful not to give great credit to Mr. Thatcher Brown, Senior, for his untiring work as Chairman of the committee to raise $4,500,000 by public subscription. It is not generally known that he gave up business entirely for six months in order to devote himself to this campaign. When he asked to be relieved at the end of that time, all but a small part of the desired amont had been raised.

By June, 1923, the ground plans for the Medical Center had been approved and on January 21, 1925, the ground-breaking ceremonies took place, Mr. Harkness using a suitably inscribed silver spade presented to him by the architect and builders. (Later, Mrs. Harkness presented this spade to the Hospital.)

The building plans were approved April 14, 1925. Things moved fast and on March 16, 1928, there was an Opening Day when some 5,000 people inspected the new buildings.

March 26, 1928, was the day of the big move. Some fifty-three patients were transported to their new quarters without incident, Miss Maxwell being the first patient admitted. So well had everything been organized that, as Dr. Palmer wrote, "I received my mail at 70th Street in the morning and dictated the answers in my new office at 168th Street after lunch." The formal dedication took place on Columbus Day, October 12, 1928. It was a gala occasion on a beautiful October day. There were good speeches and honorary degrees were conferred by Columbia University on Edward S. Harkness, Dean Sage, Otto Eidlitz and James Gamble Rogers. The future certainly looked rosy.

About a dozen years later, when Ed Harkness was a patient in Harkness Pavilion with the beginning of what proved, unfortunately, to be his final illness, I was sitting with him in his room on one of the upper floors. It was a beautiful, sparkling winter afternoon and the view of the Hudson River, the West Side Highway and downtown New York was silencing in its beauty. As the lights came on along the Drive and in New York's tall buildings Ed Harkness turned to me and said "You know when I came up here and sat on a broken-down fence and looked at the deserted ball park, I dreamed of a hospital and medical school here" (silence for a few minutes) "but what has happened here surpasses anything I did or could dream of."

What more can one add?

Symposium on Electrolyte Metabolism

Introduction to a Symposium on Electrolyte Metabolism*

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ELECTROLYTE metabolism is not only of considerable clinical importance but also, historically, a field that has undergone great changes within the past twenty-five years. It is pleasing to add that a respectable number of significant contributions have been made by those who were students or interns at the Medical Center during this twenty-five year period.

Precise quantitative measurements are no longer mere laboratory curiosities but have become more or less routine clinical procedures. Twenty years ago the clinical chemistry laboratory of the Department of Medicine performed about 3,400 determinations in one year, while in the past year 27,200 estimations were made, about an eight-fold increase. A bewildering variety of new tests and analytical technics continue to be introduced on a research basis, many of them to become permanent fixtures in the clinic. It may therefore be of some interest to mention, in a general way, some of the developments of the past and to comment on some of our current problems.

First of all, we might recognize that the term "electrolyte metabolism" is somewhat of a misnomer. My dictionary defines metabolism as "change," more specifically as the changes associated with definite biochemical reactions. Thus the metabolism of the carbohydrates can be followed through an almost endless sequence of different carbon compounds. But such reactions are not the major concern of electrolyte metabolism. Rather, we are interested in two rather simple problems—concentration and distribution; and furthermore, we are concerned with the concentration and distribution of a very limited number of substances; first, those which are involved in the regulation of the volume and osmotic pressure of the body fluids and, secondly, those which are related to the control of hydrogen ion concentration. This definition may be somewhat narrow and undoubtedly excludes many questions of real interest but at least it emphasizes the nature of the majority of clinical problems: disturbances in volume, in osmotic pressure and in pH. These are frequently encountered; they are easy to document, easy to treat and, by the same token, easy to overtreat.

It is now commonplace to think of many of the mechanisms regulating the distribution of salt and water in terms of those physicochemical concepts which apply to dilute solutions of electrolytes. The student of today learns about the Donnan equilibrium, the Henderson-Hasselbalch equation, and so forth. Yet the description of biologic reactions in terms of these simplifying concepts is in many ways a relatively recent development, particularly in clinical medicine. And it is quite proper that we recall that one of the great pioneers in this field was a member of this institution. In his early studies, carried out not much more than twenty-five years ago, Dr. Walter W. Palmer showed how the mechanisms for acidification of the urine could be examined in terms of precise chemical concepts.

Perhaps one of the greatest advances of the last quarter century lies in the field of nomenclature. In the earlier studies all results were expressed in terms of gravimetric measurements. As is well known, electrolytes are of physiologic importance not because of their weight but by virtue of the number of particles in solution. If the housewife wanted to know the actual number of vegetables which she had in her shopping bag, she would have a difficult time if she added the weight of the peas to the weight of the watermelon. Similarly, one would learn just as little by adding the weight of serum chloride to that

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of serum albumin. But the same measurements promptly become useful when they are expressed either in terms of the number of particles present, hence the mole, or milli-mole, or in terms of the number of their charges, hence the equivalent, or milli-equivalent. The modern terminology was first introduced into clinical medicine at this hospital and is now almost universally employed.

It is also well for us to realize, especially those of us who are engaged in teaching, that not all the problems of nomenclature are solved. According to Dr. W. Mansfield Clark, in the chemical literature the term "base" has at least five different meanings, some of which the student learns about during his pre-medical training. And then in medical school, base is used to mean something quite different. When the first year student measures the serum concentration of carbon dioxide, a volatile acid, and is told that his answer is a measurement of "fixed base," it seems to me that he is entitled to a certain amount of sympathy. The terms cation and anion are quite clear and they should be more widely used.

The current interests of electrolyte metabolism can, as mentioned earlier, be considered in terms of a relatively small number of concepts. These include concentration, volume, distribution and balance—both net balance as the difference between intake and output, and also dynamic balance as measured by actual rates of exchange into or out of a given compartment. In terms of historical development, the first studies were concerned mainly with concentration, that is, the chemical composition of the blood, the urine, various tissues, etc. As some of the physiologic problems became better defined, increasing interest centered around the balance study, the measurement of over-all intake and output, interpreted in the light of the resultant changes in plasma concentration. Classical studies on diabetic acidosis and adrenal insufficiency, carried out at the Medical Center, utilized these relatively simple methods. And although this continues to be one of the most fruitful technics for clinical investigation, it is in many ways an extremely difficult and tedious procedure. To be of any significance a balance study must be well planned in advance and must be very carefully controlled. More recently, accurate measurements of the fluid compartments of the body have resulted from application of the dilution technic. Following the administration of a suitable foreign substance, its volume of distribution can be calculated from the resultant plasma concentration. By the selection of the proper test substance, quantitative estimations of the blood volume, total body water and the extracellular fluid volume can now be made, although in the latter instance there is little general agreement concerning the identity of the ideal test substance. By the same dilution principle, but with the use of labelled isotopes, it is likewise possible to measure the total amount of electrolyte within the body, or at least the amount which can equilibrate with the administered isotope. Normal values for total exchangeable sodium and potassium are now available but it is too early to evaluate their usefulness at the clinical level. Factors controlling the distribution of electrolytes within the various subdivisions of the body have also been extensively examined. In general, transfers across the capillary membrane can be adequately described in terms of relatively simple processes, such as filtration and diffusion, while transfers between the extra- and intracellular spaces, that is across the cell membranes, represent a far more complex picture. We commonly speak of the "intracellular space" as a physiologic entity. That this is an oversimplification is obvious. For if anything characterizes these cellular mechanisms it is that each cell type is a law unto itself. The more recent studies, especially with the use of isotopes, have completely revolutionized the older concepts of selective permeability. Increasing emphasis has been given to the role of active cellular metabolism in the transport of electrolytes, especially in studies in the nervous system, the red blood cell and the kidney.

And now, a few general words about therapy. In the practice of medicine it is generally held that the primary purpose of treatment is to make the patient better. If the improvement is symptomatic, well, that is fine, but certainly much more important are those instances in which a specific disease is eradicated, or in which a deleterious physiologic disturbance is corrected. This obviously applies to all aspects of medicine—even to disorders of electrolyte metabolism. But I have a feeling that a second and possibly quite different goal has crept into the picture. If the first objective is to make the patient better, the second is to make him chemically normal—normal either in terms of volume or in terms of concentration. I would suggest that a number of serious difficulties have arisen from a failure to distinguish clearly between these

two goals. Too often it has been tacitly assumed that chemical mormalcy is synonymous with clinical well-being. In terms of therapy we are dealing with two variables which we may call "clinical improvement" and "chemical improvement," and there are three possible combinations: first, simultaneous improvement in both spheres; second, chemical improvement without any clinical benefit; and third, a correction of the electrolyte abnormality but with a detrimental effect on the patient.

If we examine the first category we are reminded of a vast number of acute disturbances in which correction of the salt and water defect results in unequivocal clinical benefit. There are endless examples: acute dehydration, regardless of its cause; cholera, or the less exotic causes of diarrhea; severe diabetic acidosis; acute blood loss. The results of proper treatment have been extremely successful and we need not belabor this point further.

But when we consider the second category, the picture is less clearly defined. These are the conditions in which there is no clear-cut correlation between the chemical abnormality and the clinical picture. As an example, we may consider a problem that has been extensively studied in recent years—that of hyponatremia. Now, historically, a low serum sodium is supposed to be very bad. For instance, in the crises of Addison's disease, when the sodium deficit is corrected the patient gets better. But as more determinations have been made in recent years it has become apparent that conditions as common as some of the chronic diseases of the cardiovascular system are often associated with a low concentration of sodium in the serum. This is not the time to examine the mechanisms which produce salt depletion in these patients. The present question is, What harm does it do? The Addisonian with a serum sodium concentration of 120 mEq./L. is often critically ill. But in the other groups, the decompensated cardiacs, the chronic nephritics or the severe cirrhotics, the situation is quite different. While it is true that some of these patients may have difficulties which may be directly attributed to their hyponatremia, the suprising thing is that so many of them are quite asymptomatic. And the same thing might be said for a considerable number of patients who develop a chemically measurable potassium deficit.

The third category comprises those instances in which the patient's condition becomes worse as the electrolyte disturbance is corrected. And I am not referring just to overtreatment. Examples here are somewhat harder to find. One such instance is an occasional patient with hyperparathyroidism and a high serum calcium. When the parathyroid adenoma is removed, the serum calcium overshoots the mark and falls below normal. But sometimes a patient will develop overt tetany when the calcium value is still well within the normal range. Another example, perhaps less clear cut, is the hyponatremic cardiac. We had an opportunity to observe one patient with a serum sodium of 117 mEq./L While careful balance studies were being carried out, an attempt was made to correct the chemical abnormality by infusing hypertonic saline. After several days the study had to be abandoned; for although the serum sodium had risen only to 125 mEq./L., by this time the patient had developed such severe thirst that she was unable to tolerate our therapeutic efforts any longer. Dr. Loeb has often cited another example, the Addisonian who has gradually lost salt and water, with a secondary reduction in circulating blood volume and a comparable decrease in the muscle mass of the myocardium. When volume is suddenly restored to normal, the load becomes too great for the small heart and acute cardiac failure may result. In each of these examples rapid correction of a documented abnormality has a harmful effect although, granted, this may be only temporary.

Perhaps I have given these matters undue emphasis but I believe that a real problem has been raised by the tremendous increase in the number of measurements now available to us. When an abnormal value for the blood volume, or the serum sodium, or the serum potassium is reported, too often the first question is "How are we to get this back to normal?" I suggest that such an emphasis is wrong, that the first question should be, "What harm is this doing the patient?" I grant that it is statistically probable that a patient who has normal values, both for volume and for concentration, is better off than the patient with a demonstrable abnormality; but this is not a public health problem and statistics here may have little meaning. And I do not mean that chemical deficits should be repaired only when there is something obviously wrong with the patient, such as a systolic pressure approaching absolute zero. Certainly correction of a minor asymptomatic deficit is often indicated. Indeed, one of the most gratifying

of recent advances has been the prevention of some of these problems by the correct administration of electrolytes to those patients who have to be maintained on parenteral fluids for long periods of time.

Of course, there is one great defect in the analysis of the problem as I have presented it, and that is, I have assumed that we are able to judge whether or not the patient improves. Technics of clinical observation are relatively crude and the more controlled measurements at the experimental level are often difficult to evaluate. Indeed we know precious little about the effects of salt and water on many physiologic functions. This is not exactly a new problem. For years investigators have tried to interpret cellular functions in terms of biochemical measurements. And this is still just as much of a riddle for electrolyte metabolism as it is for some of the more esoteric branches of biochemistry.

I have previously mentioned some of the dimensions in which electrolyte metabolism can be measured: volume, concentration, et cetera. But in considering the subsequent physiologic disturbances another factor becomes evident. Whereas generalizations are dangerous, it is fair to say that, with few exceptions, those chemical abnormalities which do the most harm are associated with rather abrupt deviations from the normal. They develop rapidly and they deserve to be corrected rapidly. In contrast, when the electrolyte deficit seems out of proportion to the clinical picture, it is common for the disturbance to have developed gradually over a long period of time. To say that time permits the development of compensatory reactions is in part true but we should not let such a ponderous statement obscure the fact that we are in total ignorance of the nature of many of these compensations.

Electrolyte metabolism comes close to being an exact science. Its measurements are so precise that at times they almost become endowed with the mystical power of absolute truth, and one faces an almost irresistible temptation to treat the abnormality that is easiest to demonstrate by a laboratory test. But any single determination measures only one dimension. For example, a value for the serum sodium tells you exactly only one thing—the concentration of sodium in the serum. It does not tell you the volume in which that sodium is distributed; it does not tell you how long the sodium has been at that level; nor does it tell you the venous pressure, or the cardiac output, or the nature of any compensatory reactions. But above all, it does not tell you the number of angels that can dance on the head of a pin.

The Role of the Kidney in the Regulation of Acid-Base Metabolism*

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THE responsibility for maintaining a constant pH of the extracellular fluids is shared jointly by the kidney and lungs. As is well known, the chief buffer system of the extracellular fluid is the $NaHCO_3$: $H.HCO_3$ system. The concentration of carbonic acid in extracellular fluid is directly related to the CO_2 content of the alveolar air which in turn is determined by respiratory minute volume. Thus by changing the rate and depth of respiration the amount of buffer acid in body fluids can be rapidly altered. The respiratory responses to metabolic acidosis and alkalosis are familiar examples of the homeostatic function of the lungs in maintaining the constancy of the pH of extracellular fluid.

The chief role of the kidney in acid-base balance is to regulate the relative amount of fixed cation in extracellular fluid that is in combination with bicarbonate anion. Normally about 25 mEq. of the fixed cation of extracellular fluid is covered by the bicarbonate anion. When the alveolar CO_2 tension is normal, this amount of bicarbonate-bound cation results in an extracellular fluid of pH of 7.4. In order to maintain the normal concentration of bicarbonate-bound cation the kidney must work constantly. The electrolyte content of the average diet is far different than that of the extracellular fluid. Moreover, the oxidation of sulfur- and phosphorus-containing foods leads to the production of the fixed anions SO_4 and PO_4 which displace bicarbonate ion in extracellular fluid. To meet this challenge the kidney must continually conserve fixed cation and bicarbonate. In other words, it must take a certain proportion of the neutral salts such as NaCl and Na_2SO_4 which are filtered through the glomerulus, reclaim the sodium ion, return it to the circulation in combination with bicarbonate ion, and excrete the fixed anion in combination with some other more dispensable cation. Under more unusual circumstances the kidney may be called upon to do just the opposite, namely, to combat a threatened alkalosis by excreting fixed cation in combination with bicarbonate anion.

Inasmuch as the conservation of fixed cation by the kidney is the more common of the foregoing two problems, let us consider primarily this aspect of renal function. Three devices are employed by the kidney to return from the glomerular filtrate an adequate amount of fixed cation in combination with bicarbonate ion and to excrete into the urine the acid products of metabolism in combination with a cation other than sodium. The first is the obvious device of conserving available resources and reabsorbing completely all the filtered sodium bicarbonate. The second is the acidification of the urinary buffer salts. The third is the excretion of fixed anions in combination with NH_4^+ rather than Na^+. Until recently these three functions of the renal tubule in the control of acid-base balance were considered to be quite independent of each other although they worked admirably together to achieve a common purpose. It is now appreciate that all renal devices for the conservation of bicarbonate-bound fixed cation share a single mechanism which is fundamental to the role of the kidney in acid-base balance. This mechanism is the exchange of hydrogen ion formed in the renal tubular cell for sodium ion in the renal tubular urine, hereinafter referred to as $H^+ - Na^+$ exchange.

The Role of $H^+ - Na^+$ Exchange in the Acidification of the Urinary Buffers. One of the greatest contributions to renal physiology was the monograph of Cushny which presented succinctly what came to be known as the modern theory of renal function. Cushny appreciated the role of

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the glomerulus in filtering a large volume of extracellular fluid and that of the renal tubular cells in actively transporting back to the circulation those substances which were essential to the body economy. Cushny, however, was convinced that all the eventual constituents of the urine appeared originally in the glomerular filtrate. He envisioned renal tubular transport as being unidirectional, from renal tubular urine to tubular cell. Excretion of substances from the body was accomplished by incomplete tubular reabsorption. So completely did Cushny dominate thought in the field of renal physiology that decades were to pass before the great importance of renal tubular transport from tubular cell to tubular urine, a process also known as renal tubular secretion, was fully appreciated.

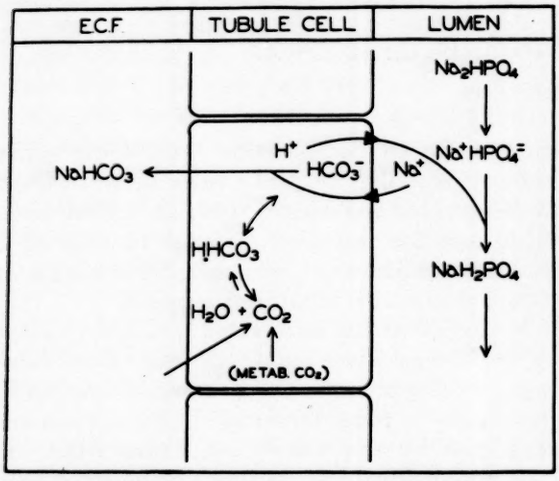


FIG. 1. Schematic representation of the role of the hydration of CO_2 and $H^+ - Na^+$ exchange in the acidification of urinary buffers.

Cushny's theory was considered quite adequate to explain the acidification of the urine and the conservation of fixed cation. Contained in the glomerular filtrate are the buffer systems of the extracellular fluid. Chief among these are Na_2HPO_4: NaH_2PO_4 and $NaHCO_3$: $H.HCO_3$. By the selective reabsorption of the basic components of these buffer systems the urine would become acid and fixed cation would be made available.

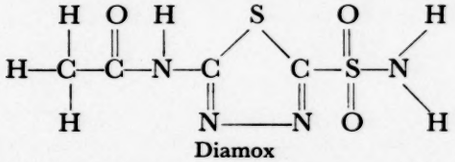
It was not until 1945 that this theory was challenged. When the challenge came it was so devastating as to demand complete discard of the filtration-reabsorption theory of the acidification of the urine. The experiments that led to this change of thought were designed by Pitts and associates.[1,2] They worked with the chief tools available to the renal physiologist for dissecting the intricate problem of tubular function, namely, the measurement of what entered the renal tubule by determining glomerular filtration rate and the composition of the glomerular filtrate, and the measurement of what left the renal tubules by determining the composition of the urine and its rate of flow. In order to gain crucial information with such gross technics experiments have to be ingeniously designed. Pitts set up conditions that would lead to urinary excretion of the maximal amount of titratable acid. He did this by giving ammonium chloride to his subjects in order to produce metabolic acidosis. He also assured the presence of adequate amounts of buffer salts in the urine by the administration of phosphate salts. Under these conditions large amounts of titratable acid appeared in the urine. It was easy to calculate that the titratable acid of the urine far exceeded that which could be accounted for by the total excretion of the more acidic components of the glomerular filtrate. Hydrogen io must have been added to the urine by the renal tubular cells.

Pitts and associates carried their concepts still farther. They postulated that the source of H^+ that was secreted by the renal tubular cells was carbonic acid. Carbonic acid can readily be formed in the cell by hydration of the CO_2 of metabolism. The enzyme carbonic anhydrase is essential for the rapid conversion of CO_2 to $H.HCO_3$. Pitts was able to demonstrate that inhibition of this enzyme by sulfanilamide decreased the titratable acidity of the urine. He therefore visualized the mechanism for the acidification of the urine as an exchange between H^+ in the tubular cell with Na^+ in the tubular urine. The Na^+ exchanged in this process would combine with HCO_3^- in the tubular cell that was made available by the secretion of H^+. In this manner $NaHCO_3$ would be returned to the extracellular fluid. The sequence of events in the acidification of the urine and the conservation of fixed cation by $H^+ - Na^+$ exchange is depicted in Figure 1.

It will be noted in Figure 1 that H^+ is shown to exchange with the Na^+ of Na_2HPO_4 to convert this compound to NaH_2PO_4. This is done to emphasize the importance of buffer salts in the acidification of the urine. It is a well known fact that the urine of man cannot become more acid than approximately pH 4.4. At this pH the hydrogen ion concentration of the urine is approximately 1,000 times greater than that of the

extracellular fluid. This concentration gradient is apparently the maximum that can be achieved by the work of the tubular cells in secreting H^+. If only the sodium salts of strong acids were present in the urine, $H^+ - Na^+$ exchange would result in the formation of a strong acid and the secretion of H^+ would soon stop. Therefore the important fact remains that the presence of buffer salts in the tubular urine is essential for excretion of maximal amounts of titratable acid and conservation of maximal amounts of fixed cation. As is well known, most of the titratable acid in the urine can be accounted for by the conversion in the renal tubule of Na_2HPO_4 to NaH_2PO_4. The classical contribution of Pitts and co-workers was to demonstrate that this was achieved by the secretion of H^+ ($H^+ - Na^+$ exchange) rather than by the selective tubular reabsorption of Na_2HPO_4.

The Role of $H^+ - Na^+$ Exchange in Bicarbonate Reabsorption. As already pointed out, one of the important mechanisms by which the kidney combats acidosis is by conserving all available resources of bicarbonate-bound fixed cation. Thus the first step in the excretion of an acid urine is the reabsorption of all filtered $NaHCO_3$. It has long been known that most of the $NaHCO_3$ of the glomerular filtrate is reabsorbed in the proximal tubule. The mechanism of the reabsorptive process was believed to involve the transport of $NaHCO_3$, as such, from tubular urine to tubular cell. It is now believed that $NaHCO_3$, *per se*, is not reabsorbed by the renal tubule, but rather this source of fixed cation is also conserved by the process of $H^+ - Na^+$ exchange. This suggestion was first made by Berliner and associates.[3] They were working, at the time, with a very potent inhibitor of carbonic anhydrase which was synthesized by Roblin and co-workers.[4] The inhibitor, known as diamox, is also a sulfonamide derivative. Its structure is shown because it promises to become an important drug for the mobilization of edema fluid.



Diamox

Berliner and co-workers observed that when diamox was given to experimental animals, not only did titratable acid disappear from the urine but also as much as 50 per cent of the sodium bicarbonate of the glomerular filtrate escaped reabsorption and was excreted. Inasmuch as diamox is highly specific in its action, the increased excretion of bicarbonate must have been due to the inhibition of carbonic anhydrase. As already explained, a lack of this enzyme would deprive the renal tubular cell of H^+ for exchange with Na^+. Since a lack of H^+ reduced both acid excretion and bicarbonate reabsorption, Berliner postulated that the fundamental mechanism for each process must be the same.

When sodium bicarbonate is present in the renal tubule the following events would occur as the result of $H^+ - Na^+$ exchange:

Tubular Cell		Tubular Urine
$H^+.HCO_3^-$		$Na^+.HCO_3^-$
	$H^+ - Na^+$ Exchange	
$Na^+.HCO_3^-$		$H^+.HCO_3^-$
		$\downarrow$
		$CO_2 + H_2O$

The CO_2 formed in the renal tubule would rapidly diffuse back into the tubular cells and the body fluids.

Convincing evidence that bicarbonate reabsorption depends on the exchange of H^+ made available from the hydration of CO_2 has been presented by Dorman, Sullivan and Pitts,[5] and Brazeau and Gilman.[6] Working independently, both groups performed almost identical experiments. They showed that by altering alveolar CO_2 tension, and hence the concentration of carbonic acid in body fluids, the amount of bicarbonate reabsorbed by the renal tubule can be markedly changed. Thus in respiratory alkalosis, when the concentration of carbonic acid in the body fluids is reduced the amount of sodium bicarbonate reabsorbed by the renal tubule is diminished and more bicarbonate anion in combination with fixed cation is excreted. In respiratory acidosis, when the concentration of carbonic acid in the body fluids is increased the reabsorption of sodium bicarbonate is greatly enhanced and its excretion diminished. Moreover, if H^+ transport and bicarbonate reabsorption are inhibited by diamox, the inhibition can be overcome by raising CO_2 tension. This procedure provides adequate amounts of $H.HCO_3$ as a source of H^+ for transport even though the amount of active carbonic anhydrase in the tubular cells is greatly decreased.

The relationship between bicarbonate reabsorption and the carbonic acid concentration

of the body fluids is shown in Figure 2. Not only do these experiments provide evidence that reabsorption of sodium bicarbonate is achieved by $H^+ - Na^+$ exchange, but they also afford insight into the mechanism by which the kidney compensates for respiratory acidosis or alkalosis by respectively increasing or decreasing the rate of tubular reabsorption of this important buffer salt.

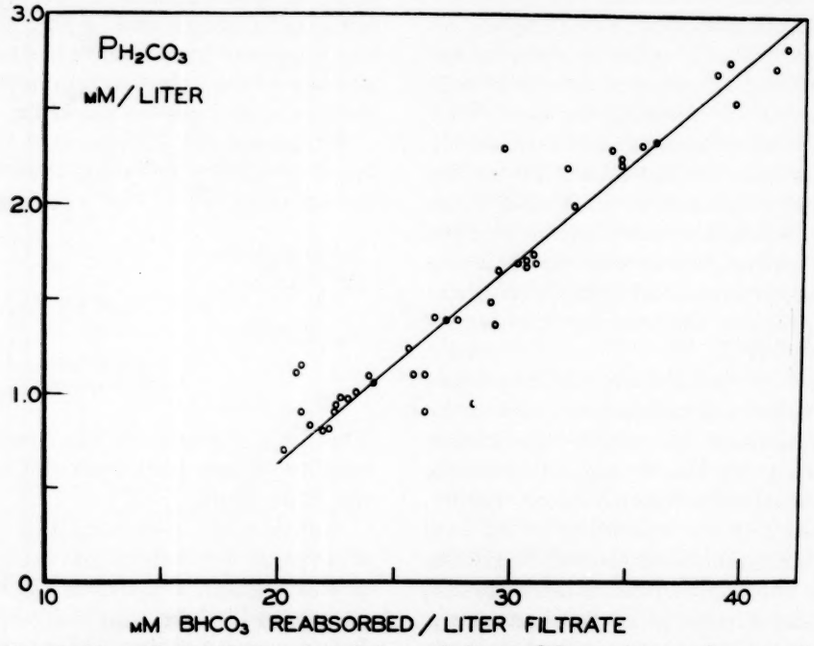


FIG. 2. The effects of induced variations of plasma CO_2 tension on the rate of reabsorption of sodium bicarbonate. (Brazeau and Gilman.[6])

A schematic representation of the tubular mechanism for bicarbonate reabsorption is presented in Figure 3. It is of interest to note that the bicarbonate ion eventually returned to the extracellular fluid in combination with sodium is not the filtered anion but rather the intracellular anion derived from the hydration of CO_2. Nevertheless the end result is the same as if $NaHCO_3$, *per se*, had been reabsorbed. The filtered HCO_3^- is converted to CO_2 which diffuses back into the tubular cell and can again be rehydrated to carbonic acid. Thus no net use of CO_2 need occur during bicarbonate reabsorption.

The Role of $H^+ - Na^+$ Exchange in the Urinary Excretion of Ammonium Salts. The final mechanism for the renal conservation of fixed cation is the substitution of NH_4^+ for Na^+ in the excretion of neutral salts. The sodium reclaimed by this process can then combine with bicarbonate ion and be returned to the extracellular fluid. It is well known that during acidosis the cells of the renal tubule readily form ammonia from glutamine and certain other amino acids and that this ammonia eventually appears as NH_4^+ in the tubular urine where it replaces Na^+. However, the mechanism of this exchange has only recently been appreciated. Again the initiating event is $H^+ - Na^+$ exchange.

To understand more easily the role of $H^+ - Na^+$ exchange in the renal excretion of NH_4^+, consider a hypothetical situation in which there are no basic buffer salts in the tubular urine other than $NaHCO_3$. Under these circumstances the sodium salts present would be chiefly $NaHCO_3$ and NaCl. The secretion of H^+ in exchange for Na^+ would readily continue until the reabsorption of bicarbonate was complete because no accumulation of H^+ would result from this process. (Fig. 3.) When only sodium chloride remained in the tubular urine, further $H^+ - Na^+$ exchange would result in the formation of hydrochloric acid and the pH of the tubular urine would rapidly fall to a level which would block any further H^+ transport. However, when ammonia is formed in the renal tubular cells, it diffuses readily into the tubular urine. If the urine is acid as a result of $H^+ - Na^+$ exchange, the NH_3 which diffuses immediately

reacts with H^+ to form NH_4^+. There are two important consequences of this reaction. First, H^+ is removed and this permits further $H^+ - Na^+$ exchange to occur. Second, NH_3 is removed and this permits more NH_3 to diffuse from tubular cell to tubular urine. In short, the two processes

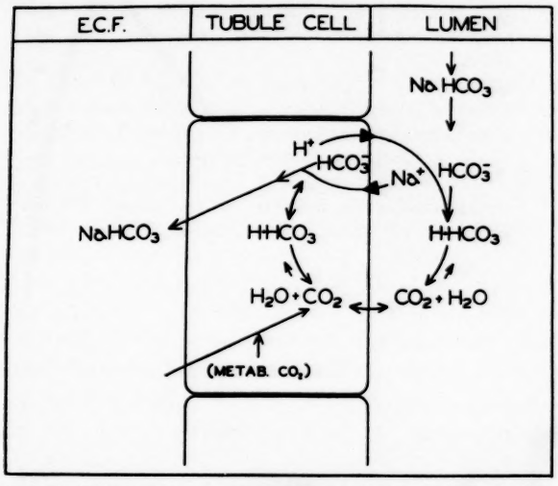


FIG. 3. Schematic representation of the role of the hydration of CO_2 and $H^+ - Na^+$ exchange in the reabsorption of sodium bicarbonate.

occur concurrently and can continue only by aiding and abetting each other. The diffusion of ammonia *removes* the concentration gradient of H^+ between tubular cells and tubular urine and permits the continuation of *active transport* of H^+. On the other hand, the active transport of H^+ *maintains* the concentration gradient of NH_3 between tubular cell and tubular urine and permits the continued *passive diffusion* of NH_3.

This sequence of events is depicted in Figure 4. Again the hydration of CO_2 to $H.HCO_3$ provides both the H^+ for exchange with Na^+ and the HCO_3^- to accompany sodium back to the extracellular fluid. By this sequence of events large amounts of sodium bicarbonate can be retrieved from neutral salts.

Proof of the importance of $H^+ - Na^+$ exchange in the urinary excretion of ammonia is provided by a relatively simple experiment. In an acidotic animal the urine contains large amounts of titratable acid and ammonium salts. If such an animal is given diamox, the secretion of H^+ is greatly diminished and the urine becomes alkaline. Under these circumstances the NH_4^+ content of the urine falls sharply. Although ammonia continues to be produced by the kidney, little of it can diffuse into the tubular urine if H^+ is not present to convert NH_3 to NH_4^+. This reaction is necessary to maintain a concentration gradient for the continued diffusion of NH_3.

The Significance of $H^+ - Na^+$ Exchange. The experimental evidence that has been presented indicates that the exchange of H^+ of the tubular

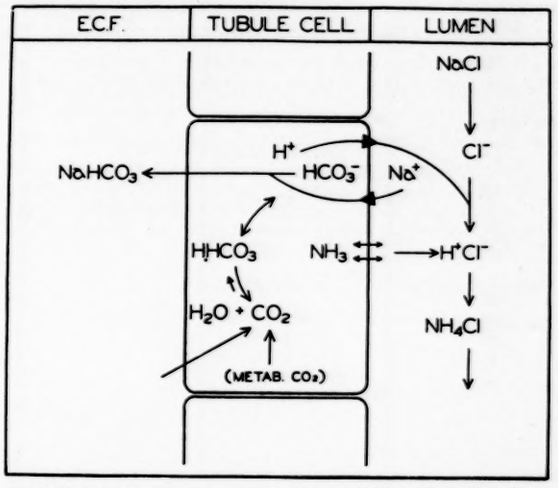


FIG. 4. Schematic representation of the role of the hydration of CO_2 and $H^+ - Na^+$ exchange in the utilization of NH_3 for the conservation of fixed cation.

cell for Na^+ of the tubular urine is the primary event in the renal control of acid-base balance. When the kidney performs this function at its maximal capacity, (1) sodium bicarbonate is completely reabsorbed, (2) the urinary buffers are acidified and (3) NH_3 is converted to NH_4^+ to make effective this important mechanism for the conservation of fixed cation. Conversely, a reduction in the rate of H^+ secretion results in the excretion of an alkaline urine. Although the events depicted in Figures 1, 3 and 4 may first seem complex, they focus attention on a single mechanism which is rather simple to comprehend. Furthermore, the effects of pCO_2 and the inhibition of carbonic anhydrase on H^+ transport indicate that carbonic acid is the chief source of H^+ in the renal tubular cell. Certainly no more dramatic disturbance of the renal control of acid-base balance can be achieved than that which follows interference with the hydration of CO_2.

However, an apodictic presentation of a single mechanism which presumably functions in all the events which are concerned with the renal regulation of acid-base balance is a vainglorious attempt of the renal physiologist to cover abysmal ignorance. For example, nothing is known of the sources of energy for $H^+ - Na^+$

exchange or the mechanisms by which this is achieved. The biochemical event by which the rate of ammonia production is attuned to the need for the conservation of fixed base is an unsolved problem. Finally, it should be recalled that the same renal cells which are secreting hydrogen ion and forming ammonia are performing dozens of other functions essential for body economy and homeostasis. Certainly this organ will continue to provide a fruitful field for investigation.

REFERENCES

1. Pitts, R. F. and Alexander, R. S. The nature of the renal tubular mechanism for acidifying the urine. *Am. J. Physiol.*, 144: 239, 1945.
2. Pitts, R. F., Lotspeich, W. D., Schiess, W. A. and Ayer, J. L. The renal regulation of acid-base balance in man. I. The nature of the mechanism for acidifying the urine. *J. Clin. Investigation*, 27: 48, 1948.
3. Berliner, R. W. Renal secretion of potassium and hydrogen ions. *Federation Proc.*, 11: 695, 1952.
4. Miller, W. H., Dessert, A. M. and Roblin, R. O., Jr. Heterocyclic sulfonamides as carbonic anhydrase inhibitors. *J. Am. Chem. Soc.*, 72: 4893, 1950.
5. Dorman, P. J., Sullivan, W. J. and Pitts, R. F. Effect of acute respiratory acidosis on renal tubular absorption of bicarbonate. *Federation Proc.*, 12: 34, 1953; *J. Clin. Investigation* (in press).
6. Brazeau, P. and Gilman, A. Effects of CO_2 tension on renal tubular bicarbonate reabsorption. *Federation Proc.*, 12: 19, 1953; *Am. J. Physiol.*, 175: 33, 1953.

Electrolyte Disturbances in Adrenal Diseases*

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THE electrolyte disturbances which accompany disorders of adrenal function may be grouped under two main headings: Those encountered in cortical hypofunction and those present in the reverse condition, cortical hyperfunction. In outline, the pattern of change in underactivity of the cortex is simple and in many respects a mirror image of that seen in over activity. The changes in both situations as reflected in the serum are set forth in diagrammatic form in Figure 1 which includes, in addition to the major serum electrolytes, a column for pH, for hematocrit and for non-protein nitrogen.

Historically, the occurrence of hemoconcentration and of some degree of renal insufficiency was recognized as a feature of adrenal insufficiency even before the changes in electrolytes were described. In 1926 Lucas[1] first reported a reduction in the serum chloride concentration and a year later Baumann and Kurland[2] noted the even more striking decrease in the serum sodium along with a moderate elevation in the serum potassium. In 1932 Loeb[3] confirmed these findings in patients with Addison's disease.

Following the demonstration of a reduced serum sodium, the problem arose as to how this depletion developed. The importance of the renal loss of this cation following adrenalectomy was first demonstrated by Loeb and Atchley[4] and confirmed by Harrop, Weinstein, Soffer and Trescher.[5] Although high potassium levels were frequently observed in experimental adrenal insufficiency, no reciprocal relationship was noted between this and the level of sodium. Darrow and others have considered that the changes in serum potassium are a reflection of decreased renal clearance of this cation which results from the decrease in blood volume and increase in hemoconcentration. Although these latter two features were an accepted part of the picture of adrenal insufficiency, it was Swingle[6] and his group who first pointed out that the degree of hemoconcentration was greater than could be anticipated from the amount of urine excreted. Darrow's[7] and Muntwyler's[8] analyses of skeletal muscle in adrenal insufficiency indicated a marked increase in the amount of fluid in the intracellular compartment. Few determinations

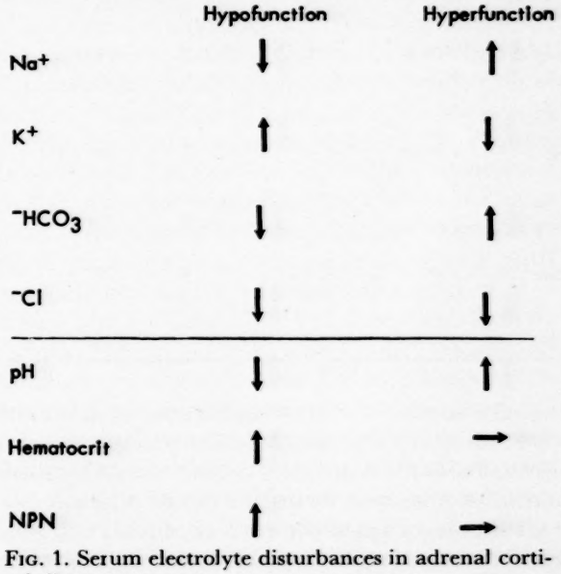

FIG. 1. Serum electrolyte disturbances in adrenal cortical disease.

of total body sodium have been made but Dr. Emily Loeb and I have found that in a state of adrenal insufficiency the carcass sodium of the rat is reduced to about 75 per cent of normal, while the potassium is increased by a considerably smaller increment.

It was Loeb who first appreciated the importance of the electrolyte disturbance as responsible for much of the symptomatology in patients with Addison's disease. Adding sodium chloride to the diet he observed a dramatic improvement in critically ill patients.[9] The addition of salt was followed by a gradual return of the electrolyte values to normal and by a fall in blood NPN, as well as by striking clinical improvement. It was

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also demonstrated that the withdrawal of salt from the diet again precipitated acute adrenal insufficiency. (Table 1.)

When potent adrenal extracts became available, Harrop[10] and others demonstrated that a state of adrenal insufficiency with chemical factor there resulted a shift of body fluids back from the intra- to the extracellular phase with concomitant increase in blood volume and renal flow. In line with this, adrenal insufficient dogs so treated consistently diuresed after an injection of extract, as might be anticipated if fluid were

TABLE 1

Date	Na (mEq./L.)	K (mEq./L.)	Cl (mEq./L.)	HCO_3 (mEq./L.)	Non-Protein Nitrogen (100 mg./100 cc.)	Blood Pressure (mm. Hg)	Remarks
July 19	123.5	5.3	88.6	21.8	39.0	85/55	Blood taken shortly after admission; profound weakness and vomiting
July 26	107.8	7.1	72.7	21.5	45.0	65/48	Critically ill; almost in extremis
Aug. 2	133.0	5.1	93.8	27.5	20.6	84/60	No more vomiting, sitting up; treated with one dose of eschatin and then NaCl
Nov. 14	139.9	4.6	107.3	24.3	20.0	112/74	Up and about at home, doing part of housework; eats 7 gm. NaCl daily plus diet; slight puffiness of eyelids
Jan. 24	126.8	5.7	92.3	21.2	35.0	86/60	After 7 days of salt-poor diet, weak and vomiting frequently; confined to bed
Jan. 30	138.0	5.0	103.5	25.9	25.0	122/80	After no further treatment except NaCl added to diet and given by rectum, no vomiting; much stronger

changes similar to those indicated in patients with Addison's disease could be precipitated in adrenalectomized animals by the withdrawal of hormonal therapy. Reinstitution of adrenal extract therapy caused the revival of such animals from a state of collapse back to normal. In this respect the animal responded to adrenal extract in a manner quite similar to intravenously administered saline with the exception, first pointed out by Stahl, Atchley and Loeb,[11] that the response to extract was much more rapid. Fifteen to thirty minutes after the administration of adrenal extract intravenously a previously moribund animal would become normally active, even though no saline has been given and before any measurable change in serum electrolytes or serum water had occurred. From this it was evident that there was some beneficial action of adrenal extract over and above that relating to the retention of sodium. Studies by Harrop, Swingle, Hartman, Darrow and, most recently, Levine, have each contributed to an understanding of this aspect of adrenal activity which is related to its protective action under conditions of stress. Harrop[12] postulated that by virtue of this mobilized from cells, and this diuresis occurred even if no fluid were administered. More recently Fritz and Levine[13] have shown that cortical hormones are necessary for the maintenance of normal vascular tone of arterioles. In their absence, these vessels lose their ability to respond normally to nor-epinephrine.

Giving large quantities of extremely potent adrenal extract, Stahl, Atchley and Loeb[11] showed that sodium withdrawal could be tolerated by adrenalectomized dogs without salt depletion; in other words, adrenal extract itself afforded adequate replacement therapy. With smaller amounts of extract, however, Harrop[14] could show an interrelationship between the available sodium in the diet and the amount of adrenal extract needed for maintenance of the adrenalectomized animal. Without extract, much larger amounts of sodium were needed to sustain the life of such a dog indefinitely; indeed, it was rarely possible to do so. Similarly, a quantity of adrenal extract which was ample to keep a dog in excellent condition became inadequate when the animal was fed a sodium-

restricted diet. Swingle[15] has maintained adrenalectomized dogs in a salt-depleted state for prolonged periods of time provided sufficient amounts of adrenal extract were given. In such animals the serum sodium remained abnormally low and some hemoconcentration was evident. It is interesting to note that when adrenal extract was withdrawn from such dogs the state of insufficiency which supervened was *not* characterized by a sodium diuresis or by a further reduction in the already lowered serum level of this cation, although the usual changes of hemoconcentration and a rising blood NPN did develop.

With this brief review of the experimental background, it is perhaps easier to understand that the electrolyte pattern exhibited by the hypoadrenal patient may be quite variable. In those in whom the disease has developed gradually the classical pattern of change as outlined in Figure 1 is most commonly seen. If the condition develops rapidly or if a patient with recognized adrenal disease under treatment becomes acutely ill, little or no derangement in electrolytes may occur and the degree of hemoconcentration and of nitrogen retention will certainly be less. Finally, if the patient has been sodium-depleted prior to the onset of an acute illness, there may be no sodium diuresis and no further fall in serum sodium level may ensue.

From the point of view of practical therapy, maintenance with whole adrenal extracts remains beyond the financial means of most patients with adrenal cortical insufficiency. Clinical management of this condition is generally carried out with one or both of the following individual cortical steroids: desoxycorticosterone acetate (DCA), first synthesized by Steiger and Reichstein in 1937,[16] and cortisone acetate, first synthesized by Sarett in 1946, later produced in quantity by Merck and Company based on Kendall's[17] method of preparation.

DCA is an extraordinarily effective sodium retainer, so much so that in the early days of clinical use instances of excessive retention of salt and water to the point of congestive failure were not uncommon. In appropriate dosages, which usually range from 0.5 to 5 mg. daily, it remains an exceedingly useful means of enabling the Addisonian patient to achieve and maintain sodium balance. It is the only replacement therapy needed in about half of the patients with hypoadrenalism for day-to-day control, although it offers little protection in situations of stress. Cortisone acetate, on the other hand, is particularly useful under conditions of stress while it possesses far less sodium-retaining activity than DCA or whole adrenal extracts. Indeed, every one of the patients with hypoadrenalism taking cortisone acetate in this clinic requires added supplements of sodium chloride to maintain normal hemodilution, serum sodium and weight.

Over the past several years an enormous body of data has accumulated relating to these two steroids, of which I shall mention but one or two aspects which have been investigated by the group working in this clinic.

In 1939 Kuhlmann, Ragan, Ferrebee, Atchley and Loeb[18] were the first to note that large doses of DCA in dogs resulted in an elevation of the serum sodium along with a reduction in the serum potassium concentration. These chemical changes were accompanied by a syndrome of polyuria, polydipsia and muscle weakness. Within the past two years Mushett, Porter and Silber[19] and Swingle's group[20] have reported a similar diabetes insipidus-like picture in dogs given large loses of cortisone acetate. Comparable electrolyte changes in patients treated with cortisone acetate were noted by Sprague et al.[21] at the Mayo Clinic. In 1941 Ferrebee, Parker, Carnes, Gerity, Atchley and Loeb[22] elaborated the study on the effects of DCA in dogs to include skeletal muscle analyses. In this tissue significant replacement of the intracellular potassium by sodium was demonstrable, this abnormality, along with the muscle weakness, being reversible by increasing the intake of potassium salts. Interestingly enough, no comparable shift in intracellular components could be demonstrated in analyses of smooth muscle.[23] The effect of cortisone in this regard has not, to my knowledge, been explored.

Clinically, DCA and cortisone acetate differ in their sodium-retaining capacity. Over the past year Emily Loeb, Stoerk, Mohler and I[24] have attempted to quantitate this difference as measured in the adrenalectomized rat. On a regimen of sodium restriction, daily doses of DCA of 0.08 mg. or more permit the maintenance of normal serum concentrations of sodium. Under similar experimental conditions cortisone acetate exerts no effect upon serum sodium until doses sixteen times this large, i.e., 1.25 mg. daily, are administered.

Some clues as to why the handling of the sodium ion differs under the influence of DCA from that under cortisone acetate have been pro-

vided by comparing the effect of these two steroids upon the renal function of the dog. Garrod,[25] working in this department, and others elsewhere have found that these steroids exert influences upon both glomerular filtration rates and tubular reabsorptive mechanisms. With DCA the over-all effect is one of sodium retention, whereas with cortisone acetate the effect may vary under changing experimental conditions, depending upon which of the renal actions predominates. In some patients mild sodium retention may occur while in others the steroid may cause a diuresis.

Another aspect of DCA and cortisone acetate which has particularly interested the group here has been the action of these steroids upon the blood pressure. Loeb, Atchley, Ferrebee and Ragan in 1939[26] first reported the development of hypertension in Addisonian patients treated with DCA. This is now widely recognized as a not uncommon accompaniment of DCA therapy; upon review of the patients in this clinic with hypoadrenalism currently maintained on this steroid, blood pressures in excess of 140 over 90 were found in 70 per cent. Selye[27] has particularly emphasized the accentuation of experimental DCA hypertension by provision of a high sodium chloride intake and preliminary reduction in or damage to renal tissue. However, even in the absence of demonstrable renal damage, Perera, Lowell, Loeb and I[28] observed rises in blood pressure in normal human subjects given DCA and liberal amounts of sodium chloride. Subsequently, Perera and Blood in human studies[29] and Emily Loeb, Stoerk, Seegal and myself[30] in rat experiments have shown that the hypertensive action of this particular steroid is dependent upon an adequate sodium intake, i.e., no rise in blood pressure will ensue if the diet be severely restricted in its content of this cation. In rats, cortisone acetate in doses above 1.25 mg. daily has a hypertensive effect of comparable magnitude to that seen with DCA, first pointed out by Gaudino.[31] This cortisone-induced hypertension, however, differs basically from that resulting from DCA in that it is independent of the sodium intake and also, unlike the latter, it is not accompanied by changes in serum sodium or potassium.[32] In clinical usage hypertension has been seen with cortisone therapy, but chiefly in patients with underlying renal damage.

I should now like to consider the electrolyte changes seen in adrenal *hyperfunction*, i.e., in Cushing's syndrome. In such patients an alteration in electrolyte pattern is far less consistently met with than in patients with hypofunction. In a review of thirty-eight individuals with unequivocal Cushing's syndrome followed here at the Presbyterian Hospital only seven of nineteen showed an elevation in serum sodium, (above 144 mEq./L.), two of sixteen shown significant decrease in potassium (below 3.0 mEq.) and fourteen of thirty-two showed definite elevation of the serum bicarbonate (above 32 mEq./L.). Similar changes have been reported in patients with normal adrenal glands during the course of ACTH or of cortisone therapy, and also experimentally produced by a combination of DCA and a high sodium intake, as already mentioned.

Correction of the abnormality in potassium, bicarbonate and chloride can usually be achieved by the addition of potassium. Unfortunately, in Cushing's syndrome the degree of clinical improvement which this leads to is seldom impressive, and definitive therapy must aim at reducing the amount of overactive adrenal tissue, directly by removal of a tumor, or partial resection of hyperplastic glands, or indirectly by reducing the ACTH stimulus with pituitary radiation.

In summary, the patterns of electrolyte changes seen in adrenal cortical disease are fairly well established. In *hypofunction* there is a reduction in the serum sodium and a less marked decrease in the serum chlorides or bicarbonate, or both. The serum potassium may be elevated although this finding is less consistently met with than the change in sodium and chloride. The bicarbonate is usually reduced. In *hyperfunction* changes in serum electrolytes occur infrequently but when present are, with the exception of the chloride ion, mirror images of those seen in hypofunction.

These electrolyte abnormalities stem from disturbances in two important features of adrenal function: (1) A mechanism for the maintenance of a normal and constant concentration of sodium ion in the body. In the absence of adrenal hormones the body becomes depleted of sodium, principally by loss through the kidney, also by loss through sweat. When hyperfunction of the adrenal cortex is present, imbalance of this mechanism results in retention of abnormal amounts of sodium which, in turn, may lead to excessive retention of fluid. (2) A second less well defined but equally important mechanism is that for maintaining a normal relationship between intra- and extracellular fluids and

for maintaining normal vascular tone. Lacking the adrenal hormones, progressive hemoconcentration and shock develop and secondarily the serum potassium rises. In what manner this mechanism is disturbed in hyperadrenal states is not at present known. It is tempting to postulate that it plays a role in the development of the hypertension which almost uniformly occurs in Cushing's syndrome.

Although several sites of action of the adrenal hormones have been localized, much remains to complete our understanding of the action of these hormones upon metabolism of the renal tubules or of the arterioles. Continued investigation of these problems is currently in progress and the information gained therefrom should increase our ability to deal intelligently with electrolyte disturbances as they occur clinically.

REFERENCES

1. Lucas, G. H. W. Blood and urine findings in desuprarenalectomized dogs. *Am. J. Physiol.*, 77: 114–125, 1926.
2. Baumann, E. J. and Kurland, S. Changes in the inorganic constituents of blood in suprarenalectomized cats and rabbits. *J. Biol. Chem.*, 71: 281–302, 1927.
3. Loeb, R. F. Chemical changes in the blood in Addison's disease. *Science*, 76: 420, 1932.
4. Loeb, R. F., Atchley, D. W., Benedict, E. M. and Leland, J. Electrolyte balance studies in adrenalectomized dogs with particular reference to the excretion of sodium. *J. Exper. Med.*, 57: 775–792, 1933.
5. Harrop, G. A., Weinstein, A., Soffer, L. J. and Trescher, J. H. Studies on the suprarenal cortex. II. Metabolism, circulation and blood concentration during suprarenal insufficiency in the dog. *J. Exper. Med.*, 58: 1–16, 1933.
6. Swingle, W. W., Pfiffner, J. J., Vars, H. M., Bott, P. A. and Parkins, W. M. The function of the adrenal cortical hormone and the cause of death from adrenal insufficiency. *Science*, 77: 58–64, 1933.
7. Darrow, D. C., Harrison, H. E. and Toffel, M. Tissue electrolytes in adrenal insufficiency. *J. Biol. Chem.*, 130: 487–502, 1939.
8. Muntwyler, E., Mellors, R. C., Mautz, F. R. and Mangun, G. H. Electrolyte and water exchange between skeletal muscle and blood in adrenal insufficiency. *J. Biol. Chem.*, 134: 367–387, 1940.
9. Loeb, R. F. Effect of sodium chloride in treatment of a patient with Addison's disease. *Proc. Soc. Exper. Biol. & Med.*, 30: 808–812, 1933.
10. Harrop, G. A. and Weinstein, A. Studies on the suprarenal cortex. I. Cortical suprarenal insufficiency and the action of the cortical hormone upon the normal and the suprarenalectomized dog. *J. Exper. Med.*, 57: 305–333, 1933.
11. Stahl, J., Atchley, D. W. and Loeb, R. F. Observations on adrenal insufficiency. *J. Clin. Investigation*, 15: 41–46, 1936.
12. Harrop, G. A. The influence of the adrenal cortex upon the distribution of body water. *Bull. Johns Hopkins Hosp.*, 59: 11–24, 1936.
13. Fritz, I. and Levine, R. Action of the adrenal cortical steroids and nor-epinephrine on vascular responses of stress in adrenalectomized rats. *Am. J. Physiol.*, 165: 456–465, 1951.
14. Harrop, G. A., Soffer, L. J., Ellsworth, R. and Trescher, J. H. Studies on the suprarenal cortex. III. Plasma electrolytes and electrolyte excretion during suprarenal insufficiency in the dog. *J. Exper. Med.*, 58: 17–38, 1933.
15. Swingle, W. W., Parkins, W. M., Taylor, A. R. and Hays, H. W. Relation of serum sodium and chloride levels to alterations of body water in the intact and adrenalectomized dog, and the influence of adrenal cortical hormone upon fluid distribution. *Am. J. Physiol.*, 116: 438–445, 1936.
16. Steiger, M. and Reichstein, T. Desoxy-corticosteron (21-oxy-progesteron) aus Delta^5-3-oxy-aetio-cholensaure (XII. Mitteilung über Bestandteile der Nebennieren-Rinde). *Helvet. chim. acta*, 20: 1164–1179, 1937.
17. Kendall, E. C. Steroids derived from the bile acids: 3,9-epoxy-Δ^{11}-cholenic acid, an intermediate in the partial synthesis of dehydrocorticosterone. *Recent Progr. Hormone Research*, 1: 65–81, 1947.
18. Kuhlmann, D., Ragan, C. A., Ferrebee, J. W., Atchley, D. W. and Loeb, R. F. Toxic effects of desoxycorticosterone esters in dogs. *Science*, 90: 496, 1939.
19. Mushett, C. H., Porter, C. C. and Silber, R. N. Effects of cortisone administered subcutaneously and orally in dogs. *Federation Proc.*, 10: 366, 1951.
20. Swingle, W. W., Fedor, E. J., Ben, M., Maxwell, R., Baker, C. and Barlow, G. Induction of diabetes insipidus in adrenalectomized dogs with cortisone. *Proc. Soc. Exper. Biol. & Med.*, 82: 571–573, 1953.
21. Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F. Observations on the physiologic effects of cortisone and ACTH in man. *Arch. Int. Med.*, 85: 199–259, 1950.
22. Ferrebee, J. W., Parker, D., Carnes, W., Gerity, M., Atchley, D. and Loeb, R. Certain effects of desoxycorticosterone. The development of "diabetes insipidus" and the replacement of muscle potassium by sodium in normal dogs. *Am. J. Physiol.*, 135: 230–237, 1942.
23. Unpublished observations.
24. Knowlton, A. I., Loeb, E. N., Stoerk, H. C. and Mohler, W. C. The combined effect of cortisone acetate and desoxycorticosterone acetate in adrenalectomized rats on a low sodium diet. *J. Clin. Investigation*, 32: 1175, 1953.
25. Garrod, O. Personal communication.
26. Loeb, R. F., Atchley, D. W., Ferrebee, J. W. and Ragan, C. Observations on the effect of desoxycorticosterone esters and progesterone in patients with Addison's disease. *Tr. A. Am. Physicians*, 54: 285–296, 1939.
27. Selye, H., Hall, C. E. and Rowley, E. M. Malig-

nant hypertension produced by treatment with desoxycorticosterone acetate and sodium chloride. *Canad. M. A. J.*, 49: 88–92, 1943.

28. Perera, G. A., Knowlton, A. I., Lowell, A. and Loeb, R. F. Effect of desoxycorticosterone acetate on the blood pressure of man. *J. A. M. A.*, 125: 1030–1035, 1944.
29. Perera, G. A. and Blood, D. W. The relationship of sodium chloride to hypertension. *J Clin. Investigation*, 26: 1109–1118, 1947.
30. Knowlton, A. I., Loeb, E. N., Stoerk, H. C. and Seegal, B. C. Desoxycorticosterone acetate. The potentiation of its activity by sodium chloride. *J. Exper. Med.*, 85, 187–198, 1947.
31. Gaudino, N. M. Las suprarenales en las hipertension arterial nefrogena. *Rev. Soc. org. biol.*, 20: 470–487, 1944.
32. Knowlton, A. I., Loeb, E. N., Stoerk, H. C., White, J. P. and Heffernan, J. F. Induction of arterial hypertension in normal and adrenalectomized rats given cortisone acetate. *J. Exper. Med.*, 96: 187–205, 1952.

Sweat Electrolyte Disturbances Associated with Childhood Pancreatic Disease*

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THE observations reported here relate chiefly to fibrocystic disease of the pancreas, a disorder which until recently was of concern primarily to the pediatrician. However, two features of the findings to be reported make them of more general implication. As will be shown, the abnormalities of sweat in these children lead occasionally in hot weather to a syndrome of salt depletion which is not related to renal or adrenal disease. Furthermore, it will be shown that the defect in the sweating mechanism may occur in members of families of these patients without demonstrable pancreatic involvement. The title of this report may therefore be somewhat misleading since the emphasis is not on pancreatic disease as such. On the contrary, our main concern has been to exclude the pancreatic phase of this condition as the cause of the electrolyte disturbance.

From the first complete description of cystic fibrosis of the pancreas in 1938 by Dorothy H. Andersen,[1] it has been recognized as a disease of more than one organ system. The pancreatic pathology, limited to the exocrine tissue, leads to the expected digestive disturbances without diabetes. More dangerous to the patients is the nearly universal bronchial and pulmonary involvement consisting of obstructive emphysema and secondary bronchopneumonia. Much less commonly, cirrhosis of the liver with portal hypertension and hypersplenism has been observed.

Since it had already been noted that patients with this disease respond adversely to periods of high atmospheric temperature,[2] it was not unreasonable to seek to implicate another glandular system in this protean disease, namely, the sweat glands. This report will summarize our previously reported measurements of the amount and electrolyte composition of sweat collected from patients with fibrocystic disease of the pancreas.[3,4] Also included are observations tending to exclude the contribution of renal and adrenal mechanisms to this picture. This summary will be supplemented by more recent unpublished observations on the familial incidence of sweat abnormalities and their possible association with chronic pulmonary disease occurring without pancreatic involvement.

SELECTION OF CASES AND METHODS

Three groups of patients were studied: fifty children with cystic fibrosis of the pancreas, ranging in age from two to seventeen years, nine patients with other diseases of the pancreas, from ten to sixty-four years in age, and fifty control cases from one and a half to forty-five years in age.

Of the first group, forty-four presented the classic clinical and laboratory features of cystic fibrosis of the pancreas. In all of them one or more duodenal assays had shown the absence of pancreatic enzymes. In the remaining six of the fifty patients the diagnosis was strongly suspected on the basis of the family history and the clinical and laboratory findings, even though some pancreatic activity was present at some time during the course of the disease. Four of the patients in the first group and two in the second have died since the sweat studies were performed and the diagnosis of fibrocystic disease of the pancreas was confirmed at autopsy.

The nine patients with miscellaneous diseases of the pancreas included four patients after total pancreatectomy; one case with a partial pancreatectomy and pancreatitis in the remaining pancreas and one of chronic recurrent pancreati-

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tis with lithiasis (all of these had diabetes mellitus); two additional patients with the usual form of diabetes mellitus; and one with an islet cell adenoma of the pancreas.

The fifty controls represented a variety of cases on the wards of Babies and Presbyterian Hospitals with the following specifically excluded: patients with known adrenal insufficiency (Addison's disease), or acute or chronic renal disease, and members of the families of known patients with cystic fibrosis of the pancreas.

No patient in any of the three groups had received ACTH or cortisone, or salicylates in the few weeks preceding the "sweat test," and none had fever at the time.

Each patient was subjected to a similar and very mild thermal stimulus while lying quietly on a bed in a room at a constant temperature of 90°F. and 50 per cent humidity. Sweat was collected in all instances from the mid-abdominal area by means of a gauze patch of known surface area protected against evaporation by impermeable plastic and sealed at the edges by waterproof adhesive tape. After a period of collection of one to two hours the gauze square was removed, immediately placed in a stoppered flask, which was then re-weighed, the gauze patch having been weighed in the dry state. A known amount of $LiSO_4$ solution was then added to the flask and aliquots analyzed for chlorides by the method of Keys and sodium and potassium by the flame photometer.

RESULTS

Abnormal Electrolyte Composition of Sweat in Cystic Fibrosis of the Pancreas. The results in terms of the chloride and sodium concentration of abdominal sweat in both fibrocystic patients and controls are summarized graphically in Figure 1. For the sake of clarity, patients with pancreatic diseases other than cystic fibrosis have been included in this figure among the controls.

The markedly increased electrolyte concentration of sweat in fibrocystic patients as compared with others is high lighted and the wide range of spread in values for both groups is likewise shown. The range for abdominal sweat chlorides for patients with cystic fibrosis of the pancreas was from 60 to 160 mEq./L. of sweat, with a mean value of 106; for the controls, from 4 to 80 with an average of 32. The corresponding sodium values were from 80 to 190 mEq., with a mean of 133, for the first group; and from 10 to 120 mEq., with a mean of 59, for the second. The overlap in chloride values was very slight; it was a little greater in the case of the sweat sodium levels. The potassium content of sweat in the two groups is not indicated on the chart but it was also increased in fibrocystic patients as compared with controls. All of these differences on analysis were of great statistical significance.

In contrast, the volume of sweat as gauged by the weight in grams per hour was not significantly different in the two groups.

Lack of effect of pancreatic or chronic pulmonary disease per se on electrolyte composition of sweat: One of the first questions to arise is whether or not pancreatic deficiency or chronic pulmonary disease *per se* can affect the electrolyte composition of sweat.

In order to answer this question patients with cystic fibrosis of the pancreas were divided into four groups. Group I represented thirty-three patients with severe pulmonary involvement and complete pancreatic achylia, by far the most common combination; group II, eleven cases with complete pancreatic deficiency but little or no pulmonary involvement; group III, four patients with severe pulmonary disease but partial or normal pancreatic function; and the last, group IV, two cases in which severe respiratory disease preceded by months or years the involvement of the pancreas. The mean values for sweat chloride, sodium and potassium in each of these groups did not differ significantly from the mean values for these electrolytes in the sweat for the group of fibrocystic disease patients as a whole.

The nine patients with the various pancreatic disorders previously described, and the eleven patients who had chronic pulmonary disease other than cystic fibrosis of the pancreas, had mean values for sweat electrolytes that did not differ significantly from the averages for all of the sixty controls.

Normality of renal and adrenal function in cystic fibrosis of the pancreas: The other two main questions to be answered concerned kidney and adrenal function in patients with cystic fibrosis of the pancreas, as impaired function in either of these two organs could conceivably lead to increase of electrolytes in the sweat.

Two patients with cystic fibrosis of the pancreas were studied under rigid metabolic conditions. Both of the subjects were prepubertal males fourteen years of age. In order to have a

complete picture of the total salt and water balance in one of these patients, C. J., the following data are recorded in Figure 2: weight in kilograms, twenty-four-hour urine output in cubic centimeters, sodium and potassium content of both urine and feces in milliequivalents per sodium but were omitted from this chart for the sake of clarity.

The patient was kept on a diet containing 85 mEq. of sodium chloride per day for an introductory period of ten days (broken line) and the salt intake was then dropped to 15 mEq. per

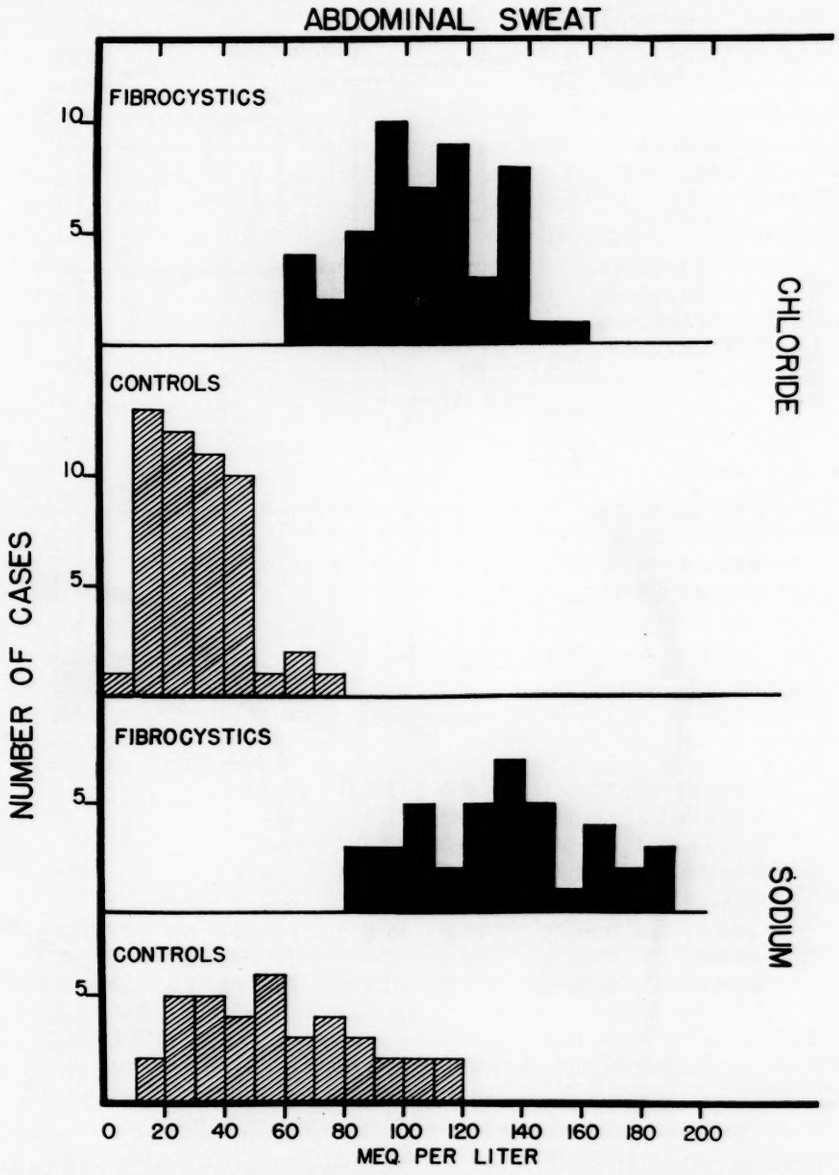


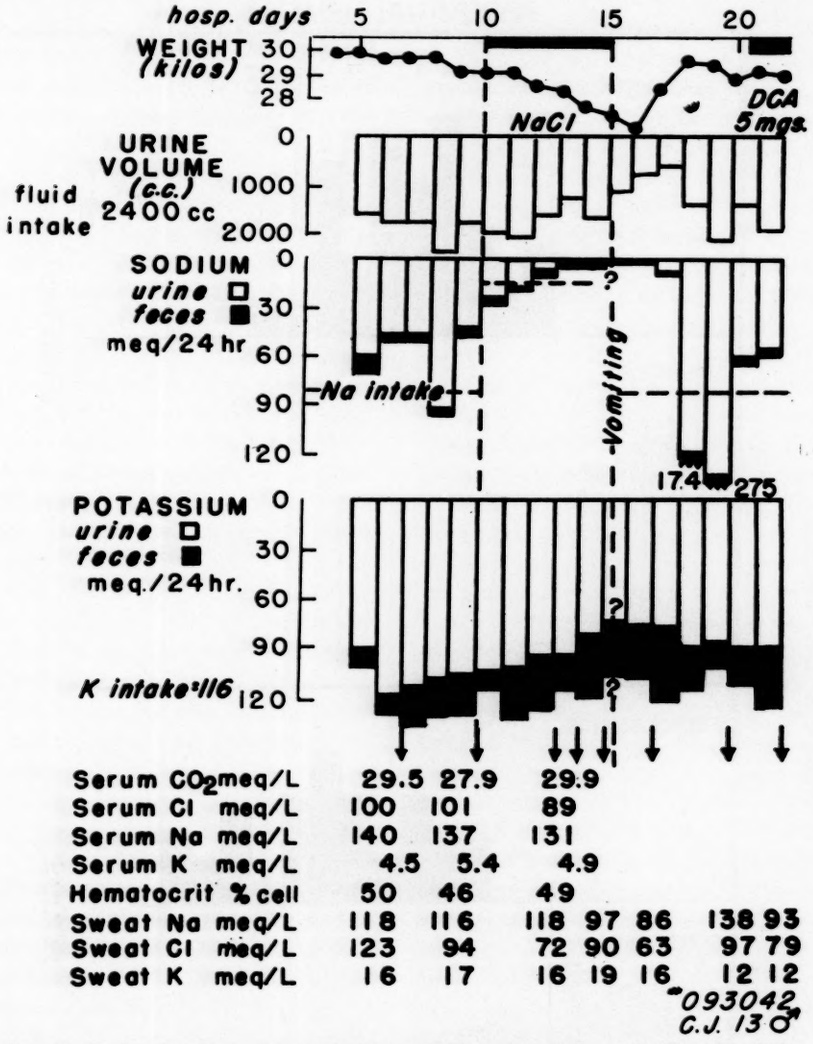
FIG. 1. Abdominal sweat chloride and sodium in patients with fibrocystic disease of the pancreas and in control cases representing a variety of other types of diseases.

twenty-four hours and, in the lower part of the same chart, the values for both serum and sweat electrolytes in milliequivalents per liter. Chlorides in both urine and feces were also determined and paralleled in all ways the changes in day. After only five days of restricted salt intake the patient had lost 2 kg. in body weight (presumably extracellular fluid), his serum electrolytes had begun to decrease and he began to vomit. The experiment was then discontinued.

During this time the kidney function as judged by the ability to conserve salt in the urine was excellent and by the third day of salt restriction the patient was losing less sodium chloride in his urines and stools combined than he was taking by mouth. Serial sweat electrolyte determinations during the whole metabolic period showed that while the values for sweat chloride, sodium and potassium decreased somewhat, they still remained in the abnormally high range. It is clear that the loss of salt by this avenue must have been great.

Similar experiments in the other fourteen-year old fibrocystic patient yielded identical results; a kidney and sweat response in all ways similar to the one described was observed as a consequence of hot weather (room temperature 90°F.) in a period in which salt intake was not restricted. Here again, large amounts of sodium chloride must have been lost through the sweat.

From the work of Conn[5] and others it is known that sweat electrolyte concentration may be increased in adrenal insufficiency (Addison's disease) and that by administering desoxycorticosterone acetate (DCA) in adequate amounts these levels may be reduced to normal. Similar results obtain in normal individuals following administration of ACTH. Accordingly, adrenal function was investigated in the two patients mentioned and judged to be normal on the basis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Na intake
vomiting
17.4
27.5
POTASSIUM urine □ feces ■ meq./24 hr. 0 30 60 90 120
K intake 116
Serum CO2 meq/L 29.5 27.9 29.9
Serum Cl meq/L 100 101 89
Serum Na meq/L 140 137 131
Serum K meq/L 4.5 5.4 4.9
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FIG. 2. C. J., thirteen and one-half year old male, with cystic fibrosis of the pancreas. Excellent response of renal mechanisms and failure of sweat to conserve sodium chloride during salt restriction (10–15 hospital day).[4]

of the following observations: normal response of the adrenal to administration of ACTH in terms of increased production of urinary 17-ketosteroids and drop in total fasting eosinophil count. When DCA was administered to one of these patients sweat electrolyte levels decreased a little but remained in the abnormally high range. This inadequate response in sweat electrolyte levels to DCA, in addition to the similarly insufficient response to hot weather and to salt restriction, pointed to a defect in the sweat glands themselves.

Acute Salt Loss in Cystic Fibrosis of Pancreas. Abnormally high electrolyte levels in sweat, combined with a volume of sweat production which is not reduced, will inevitably lead under appropriate circumstances to acute salt loss. As shown by Marriott,[6] when 0.5 to 0.75 gm. of sodium chloride are lost per kilogram of body weight, vomiting is apt to ensue and was in fact noted in all of the patients with cystic fibrosis of the pancreas under these circumstances. What had begun as a "pure salt depletion" becomes, with the onset of vomiting, a "mixed water and salt depletion" and the dehydration consequent on the salt loss is made markedly worse. Because of the rapidity of events the intracellular fluid is not greatly affected, while the extracellular fluid volume is markedly contracted.[7–9] Peripheral vascular collapse, hyperpyrexia, coma and death follow in rapid succession.

Nine patients with fibrocystic disease of the pancreas in acute salt depletion were studied on the wards of the Babies Hospital. Serum electrolyte levels were reduced in all, serum chloride values ranging from 72 to 89 mEq./L. and those for sodium between 127 and 130 mEq. In all of them, CO_2 levels in the serum were within normal limits. All of the patients were markedly dehydrated and vomiting. Only two, the most severe ones, had peripheral vascular collapse and hyperpyrexia. One of these was already in coma and close to death. They all responded with gratifying speed to intravenous administration of physiologic saline solution, although in the case of the child who had been admitted moribund and in coma the sensorium remained cloudy for several days and there was evidence of severe renal damage persisting for several days when his fluid balance had been restored.

Occurrence of Electrolyte Abnormalities of Sweat in Other Members of Families of Patients with Cystic Fibrosis of the Pancreas. Sixty members of eighteen families of twenty children known to have fibrocystic disease of the pancreas (with the exclusion of the patients themselves) were investigated by means of the "sweat test." In thirteen of these families it was possible to investigate father, mother and all of the siblings of the patients. In the remaining five families one or more members were not studied.

The sweat chloride and sodium for the group as a whole (excluding the known fibrocystic patients) differed significantly from those of sixty controls, children and adults ($P = < 0.01$). While forty-six individuals in such families had sweat electrolytes within normal limits, fourteen had abnormally high values although somewhat below the averages for patients with the manifest disease. Furthermore, four families accounted for ten of these subjects, so that some families apparently had several members with abnormal sweat while others had none outside the patient with known cystic fibrosis of the pancreas. There was no evidence of any difficulty in water and salt balance in any of the fourteen subjects.

It has been mentioned previously that generalized obstructive emphysema, at times with severe secondary bronchopneumonia, is characteristic of virtually all patients with cystic fibrosis of the pancreas,[10] perhaps because of the production of an abnormal secretion by the bronchial glands. Among the fourteen family members with abnormally high sweat electrolytes there were six who were unusually susceptible to severe and long-lasting upper respiratory and bronchial infections. In three of these generalized obstructive emphysema with varying degrees of secondary bronchopneumonia could be demonstrated roentgenographically.

Figure 3 is offered as an example of one such family tree. Co. J., age fourteen years, was known to have cystic fibrosis of the pancreas. Duodenal drainage had shown an absence of pancreatic enzymes, sweat electrolytes were abnormally high, and there was steatorrhea and azotorrhea on chemical analysis of the stools. Serial roentgenograms of the chest over a period of many years had shown generalized obstructive emphysema and chronic bronchopneumonia. The patient's father, Wm. J., Sr., age forty-four years, was found to have generalized obstructive emphysema with increasing dyspnea since the age of thirty-seven years, and a constant non-productive cough particularly troublesome in the early morning. His sweat electrolytes were abnormally high, although in the lower range for patients with fibrocystic disease of the pancreas.

Pancreatic trypsin on duodenal assay was found to be in the normal range. E. J., seven years of age, although well developed and nourished, with no intestinal complaints, and with normal tryptic activity in the duodenal content, was subject to repeated attacks of bronchial infection and subsequently was found to have generalized

The defect must therefore be in the sweat glands themselves, especially in view of their failure to conserve salt in hot weather, in periods of salt restriction and under administration of DCA. In interesting contrast, the rate of sweating was not significantly different in fibrocystic as compared with other patients.

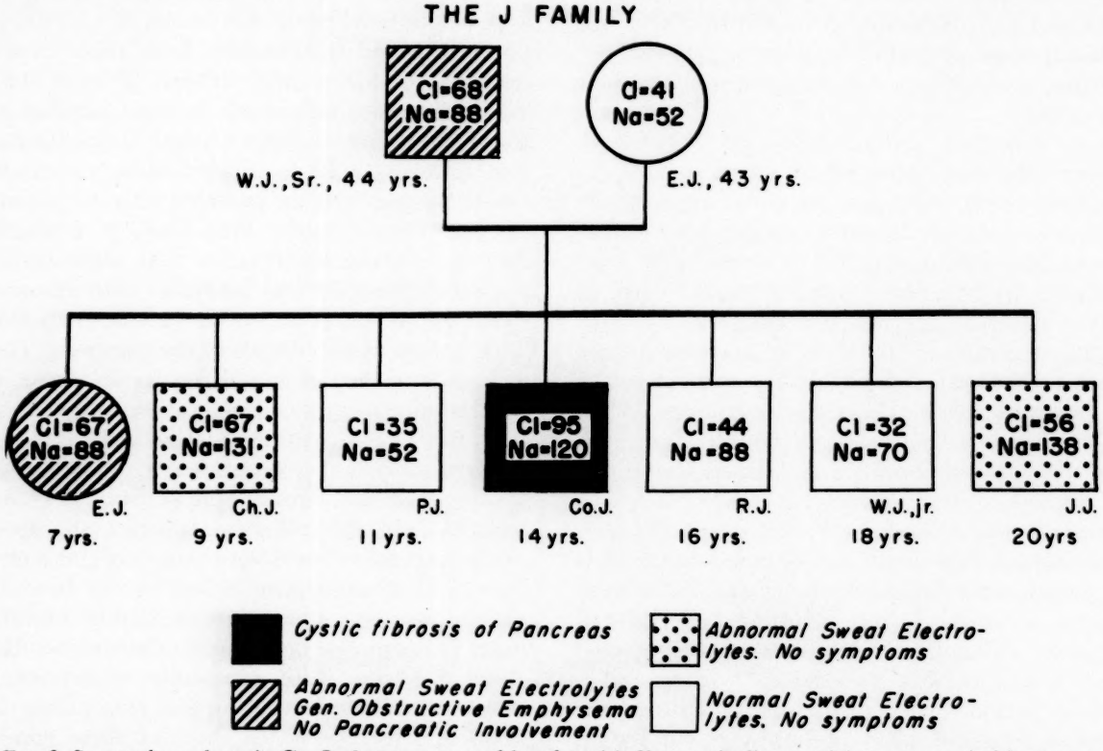

FIG. 3. Sweat electrolytes in Co. J., fourteen year old male, with fibrocystic disease of the pancreas in his parents and siblings. Note the association in two cases of abnormally high sweat electrolytes with generalized obstructive emphysema despite lack of pancreatic involvement.

obstructive emphysema and at times secondary bronchopneumonia. Two other siblings of this patient, Ch. J. and J. J., had abnormally high sweat electrolytes but no other symptoms, although J. J. was subject to frequent and prolonged episodes of bronchial infection. The patient's mother and two other siblings, P. J. and R. J., had normal sweat electrolytes and no other abnormal symptoms.

DISCUSSION

The abnormally high levels of chloride, sodium and potassium in the sweat of patients with fibrocystic disease of the pancreas, above that of almost any other type of disease, was shown not to be secondary to pancreatic deficiency or chronic pulmonary disease, while renal and adrenal function in such patients was not deranged.

The low levels of chloride and sodium in the urine, in combination with marked increases of these electrolytes in the sweat, provide a striking example of complete dissociation in the electrolyte concentration of these two fluids usually known to vary simultaneously and in the same direction. It is evident that the electrolyte composition of sweat is controlled by several different factors, some of which are poorly understood.

The mean values for chloride and sodium in sweat in patients with cystic fibrosis of the pancreas approaches the values for these electrolytes in the serum, consequently profuse sweating will lead to massive salt depletion unless replaced by heavy salt intake. Heat therefore acts only indirectly, by initiating a series of events which occur so rapidly that intracellular fluid presumably is not affected. By the time serum electrolyte val-

ues have decreased, marked reduction in extracellular fluid volume has occurred. Hyperpyrexia is a late occurrence, presumably a result of peripheral vascular collapse, and is an indication that patients have reached a critical stage and that a threat to their life has become imminent. Full appreciation of this state as an acute medical emergency in which physiologic saline solution must be administered intravenously without delay and in large amounts will permit the saving of life in the great majority of cases.

The situation occurring during episodes of hot weather in patients with cystic fibrosis of the pancreas was duplicated during the war by British soldiers in India,[6] who received liberal allowances of unsalted water while losing salt through profuse sweating. The complete freedom of muscular cramps in this group as well as in all of the fibrocystic patients was remarkable and suggests that salt depletion alone is not sufficient to cause spasmodic muscular contractions.

As the name cystic fibrosis of the pancreas implies, emphasis was placed initially on the pancreatic lesions. The frequency of bronchial involvement was soon recognized and it was postulated by some that a disturbance in the mucus-producing organs led to an abnormal secretion accounting for the pancreatic and respiratory lesions, thought to be secondary to obstruction. The demonstration that sweat glands are affected in this condition, in addition to the pancreas, lungs, liver and other organs, reaffirms that it is a generalized disease in which many or perhaps all exocrine glands are affected whether or not they are mucus-producing.

Because of the paucity of observations, the finding of a sweat electrolyte abnormality in family members similar to that of known patients with the disease, though interesting, should be interpreted with caution. The occurrence in three such cases of demonstrable generalized bronchial obstruction with secondary bronchopneumonia, which is characteristic of fibrocystic patients, also raises questions for subsequent investigations. Speculation is justified as to the occurrence of incomplete forms of the disease without pancreatic involvement and of its relation to some cases in both children and adults of chronic pulmonary disease characterized by chronic obstructive emphysema.

SUMMARY

The abdominal sweat content of chloride, sodium and potassium was found to be markedly increased in fifty patients with fibrocystic disease of the pancreas as compared with sixty control cases representing a variety of other diseases. The rate of sweating was not significantly different in the two groups.

The abnormal increase in sweat electrolyte levels in patients with cystic fibrosis of the pancreas was shown not to be secondary to pancreatic deficiency or to chronic pulmonary disease. Renal and adrenal function in respect to sodium chloride was found to be normal in fibrocystic patients studied under rigidly controlled metabolic conditions. The defect must therefore be in the sweat glands themselves.

In hot weather the abnormally high electrolyte levels in the sweat lead at times to massive salt depletion followed by peripheral vascular collapse, hyperpyrexia, coma and death. This sequence of events can be avoided by timely intravenous administration of physiologic saline solution.

Several family members of known patients with cystic fibrosis of the pancreas were found to have sweat electrolyte abnormalities similar to those described in the patients. At times these were associated with generalized obstructive emphysema, without demonstrable pancreatic involvement. This leads to speculation as to the existence of incomplete forms of the disease and their relation to certain types of chronic pulmonary disease.

While the pancreatic lesions were the first to attract attention to cystic fibrosis of the pancreas, this disorder is in reality a generalized disease in which many and perhaps all exocrine glands are affected.

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REFERENCES

1. Andersen, D. H. Cystic fibrosis of the pancreas and its relation to celiac disease. *Am. J. Dis. Child.*, 56: 244, 1938.
2. Kessler, W. R. and Andersen, D. H. Heat prostration in fibrocystic disease of the pancreas and other conditions. *Pediatrics*, 8: 648, 1952.
3. Darling, R. C., di Sant'Agnese, P. A., Perera, G. A. and Andersen, D. H. Electrolyte abnormalities of the sweat in fibrocystic disease of the pancreas. *Am. J. M. Sc.*, 225: 67, 1953.
4. di Sant'Agnese, P. A., Darling, R. C., Perera, G. A. and Shea, E. Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas; its clinical significance and relationship to the disease. *Pediatrics*, 12: 549–563, 1953.

5. Conn, J. W. Electrolyte composition of sweat. *Arch. Int. Med.*, 83: 416, 1949.
6. Marriott, H. L. Water and Salt Depletion. American Lectures in Physiology. Springfield, Ill., 1950. Charles C Thomas.
7. McCance, R. A. Experimental sodium chloride deficiency in man. *Proc. Roy. Soc., London, s.B*, 119: 245, 1936.
8. Elkington, J. R., Danowski, T. S. and Winkler, A. W. Hemodynamic changes in salt depletion and in dehydration. *J. Clin. Investigation*, 25: 120, 1946.
9. Danowski, T. S., Winkler, A. W. and Elkington, J. R. The treatment of shock due to salt depletion, comparison of the hemodynamic effects of isotonic saline, hypertonic saline and isotonic glucose solution. *J. Clin. Investigation*, 26: 130, 1946.
10. di Sant'Agnese, P. A. Bronchial obstruction with lobar atelectasis and emphysema in cystic fibrosis of the pancreas. *Pediatrics*, 12: 178, 1953.

Effect of Circulatory States on Determinations of Blood Volume*

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THE blood volume is the sum of the volume of plasma and volume of cells in the circulatory system. The technics that have been devised for estimating blood volume in the living animal or in man depend on the measurement of the volume distribution of a known amount of some suitable test substance introduced into the blood stream. The test substances fall into two categories:[1] One group, exemplified by T-1824, is distributed in the plasma. The other includes substances such as carbon monoxide which when inhaled labels the red cells, or ^{32}P with which a known quantity of red cells may be labelled and injected to determine the cell volume. The total blood volume is customarily calculated either from the measured plasma volume or from the cell volume and from the proportion of cells or plasma in the venous blood by the following simple formulas:

A. $$\frac{\text{Plasma volume} \times 100}{100 - \text{venous cell } \%} \quad \text{or}$$

$$\frac{\text{Plasma volume} \times 100}{\text{venous plasma } \%} = \text{B.V.}$$

B. $$\frac{\text{Cell volume} \times 100}{\text{venous cell } \%} = \text{B.V.}$$

It is obvious that these two calculations will not give the same answer unless the proportion of cells in the venous blood is identical with that of all the blood in the circulatory system. The values for blood volume derived in this manner must therefore be termed *estimates* rather than *measurements*. But if we determine both plasma volume and cell volume simultaneously, the sum of these may be regarded as the *measured* blood volume. Whether or not this is the true blood volume depends, of course, upon the validity of the methods employed. In the experiments to be described cell volume was measured with ^{32}P and plasma volume with T-1824. The former has been directly compared with ^{55}Fe and the results agree.[2] The fact that the volume distribution of T-1824 is identical with that of various antigens[3] of albumin[4] tagged with ^{131}I and of hemoglobin[5] constitutes strong evidence that the dye method measures the true plasma volume.

Studies on blood volume in health and disease have mostly been done with the dye method. However, in recent years a considerable number of investigations have been carried out with cell-labelling methods. For practical reasons both technics are not usually employed simultaneously. Therefore it is rather important to know where the estimates fall with relation to each other and particularly with relation to the true blood volume. In normal human subjects simultaneous measurements of plasma volume with T-1824 and cell volume with ^{32}P (see [6-9] and others), ^{55}Fe (Gibson et al.[10]) or the Ashby marked cell method[11] show that the blood volume calculated from the cell volume and the venous cell percentage is on the average[12] about 10 per cent lower than the *measured* blood volume (measured cell volume and measured plasma volume), whereas the dye blood volume is higher than the measured blood volume. Similar differences have been found in the rabbit,[13] sheep[14] and monkey[15] but in the dog the differences have not been consistent.[10,16,17] The reason for the variable results in the dog will become apparent as we consider some of the circumstances that influence the blood volume estimates derived from the dye-hematocrit and ^{32}P-hematocrit methods and see how these compare with the *measured* volume (measured cell volume + measured plasma volume).[18,19]

We may note in passing that the carbon monoxide method stands apart from the other cell-labelling methods mentioned previously. Earlier evidence to the contrary, several investigators

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have found that the CO blood volume differs little, if any, from the dye blood volume.[1] In the splenectomized dog the cell volume measured with CO is on the average 12 per cent higher[20] than that given by ^{32}P. The volume distribution of CO therefore includes more than the circulating red cells and that presumably accounts for the agreement between the CO and dye blood volume.[20] This may be regarded as a disadvantage of the CO method so far as the measurement of cell volume or blood volume is concerned, but as a tool for investigating changes in the erythropoietic tissue in the intact animal it presents interesting possibilities.

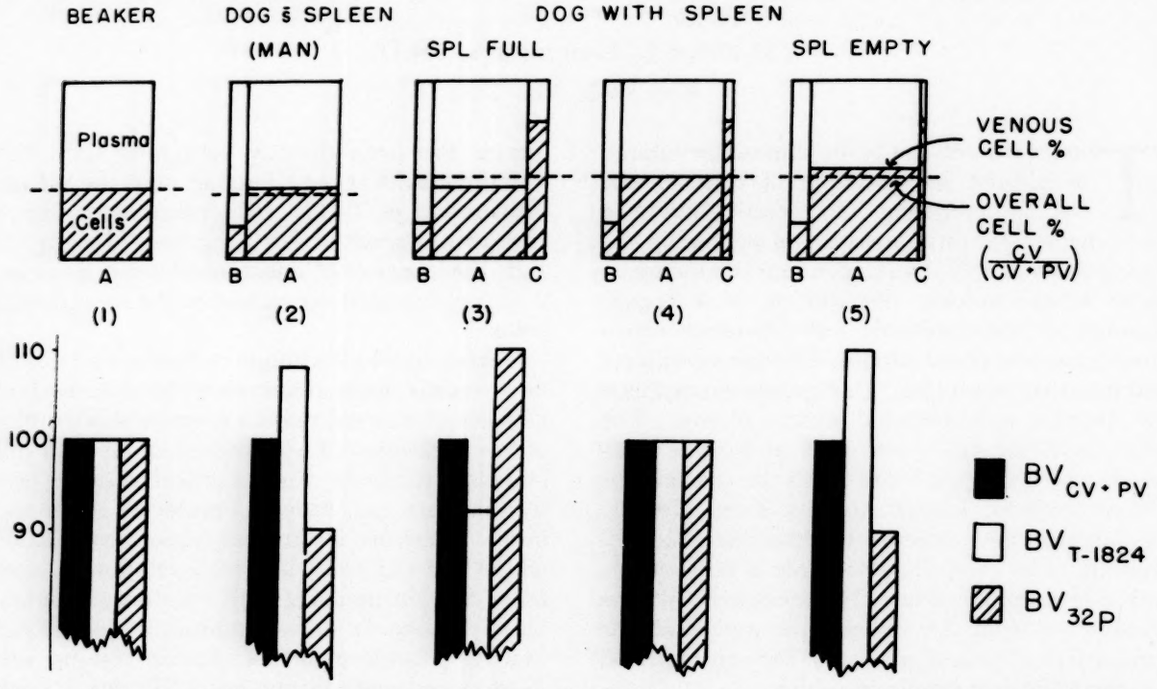


FIG. 1. Diagrammatic illustration of the effects of cell distribution on the estimates of blood volume derived from the dye-hematocrit and ^{32}P-hematocrit methods and the relation of these estimates to the true blood volume (measured cell volume + measured plasma volume).

Effect of the Distribution of Cells and Plasma on Estimations of Blood Volume with the Dye-hematocrit and the ^{32}P-hematocrit Methods.[18] The problem may be presented diagrammatically as shown in Fig. 1. The upper part of the diagram depicts several systems with the cells distributed in various ways. The lower part shows the relation of the dye-hematocrit and ^{32}P-hematocrit estimates to the *measured* blood volume (cell volume + plasma volume) in each of the systems. Blood samples for analyses are taken from compartment A and the cell percentage therein is shown by the height of the cross-hatched area. The horizontal dotted lines represent the over-all cell percentage in the systems as given by the ratio

$$\frac{CV}{CV + PV}$$

1. In the beaker the dye-hematocrit and ^{32}P-hematocrit estimates both agree with the measured blood volume, (CV + PV), because the cell percentage in the samples removed for analysis is the same as the over-all cell percentage (if the blood is properly agitated).

2. This is the simplest schema that accounts for the findings in man or in the splenectomized dog in which the cell percentage in the venous blood is higher than the over-all cell percentage. Part of the system, compartment B, contains blood with a lower cell: plasma ratio than in A, represented by venous blood. The result is that blood volume is overestimated with the dye-hematocrit method and underestimated with the ^{32}P-hematocrit procedure.

3. Here we have altered 2 by adding, on the right, a compartment (representing the dog's spleen) with a high cell percentage. The over-all cell percentage in the system is now higher than the venous cell percentage and as a result the dye-blood volume is now lower, and the ^{32}P

blood volume is now higher than the true blood volume.

4. Partial emptying of C raises the venous cell percentage and a condition may exist in which the over-all and venous cell percentages are identical. When this obtains the estimate with dye or ^{32}P is identical with the measured blood volume.

5. When C is fully emptied, the conditions are the same as in (2) except that the cell percentage in compartment A is somewhat higher. As we shall see later, and as indicated in the present diagram, this increases the overestimate of blood volume with the dye-hematocrit method.

In normal, conscious dogs with spleen intact the estimates with the dye-hematocrit and ^{32}P-hematocrit methods are on the average close to the measured volume[18] but individual tests show a wide scatter between the extremes depicted in parts (3) and (5) of Figure 1. In dogs under nembutal anesthesia, which causes relaxation of the spleen, the dye-hematocrit method consistently underestimates and the ^{32}P-hematocrit method consistently overestimates blood volume, as indicated in part (3) of Figure 1. This relation between the two estimates is promptly reversed to that shown in (5) when adrenalin is injected and the spleen contracts. It may be noted that the reversal occurs without significant changes either in measured cell volume or measured plasma volume.[18] This indicates that the observed effects on the blood volume estimates are due entirely to redistribution of cells and are not the result of a change in the volume-distribution of either T-1824 or ^{32}P. In normal, conscious dogs after injection of adrenalin the result is also consistently that shown in part (5) of the diagram. Adrenalin does not affect the relation of the *estimates* to the *measured* volume in the splenectomized dog.

It is obvious from these findings that in normal dogs with spleen intact neither the dye method nor the ^{32}P method gives a reliable or consistent value for blood volume and that this should be kept in mind in judging the results of blood volume studies on dogs. For such studies the splenectomized dog is evidently preferable.

Effects of Alterations in Blood Volume and Venous Cell Percentage on Estimations of Blood Volume. Let us now consider briefly what influence, if any, extreme circulatory disturbances have on the determinations of blood volume, for it is the estimates made under these conditions that are of special practical interest. This problem has recently been investigated in splenectomized dogs under the following conditions:[19] (1) immediately after severe hemorrhage and at intervals of days thereafter; (2) after hemorrhage followed immediately by infusion of dextran; (3) after infusions of dextran into dogs with normal blood volume; (4) after infusions of concentrated cell suspensions into dogs with normal blood volumes; (5) after three weeks acclimatization to low oxygen tension; (6) after "dehydration" with intraperitoneal dialysis or with intravenous infusions of 50 per cent sucrose, and again after "rehydration."

We may note first that the measured blood volume in normal splenectomized dogs averaged about 80 ml. per kg. body weight.[19] After severe hemorrhage the measured blood volume was reduced to as little as 50 ml. per kg. and in the dogs made plethoric by infusions of dextran or concentrated cell suspensions the measured blood volumes were in some instances raised to 120 ml. per kg. Even with these drastic changes in volume, the ratio $\frac{\text{over-all cell percentage}}{\text{venous cell percentage}}$ remained relatively constant (average 0.87), except in one group of animals in which large infusions of dextran were given immediately following severe hemorrhage. Here, for unknown reasons, the ratio was about 0.8. Except for these experiments, the underestimate of blood volume with the ^{32}P-hematocrit procedure within experimental error was independent not only of the blood volume but also of the venous cell percentage, which in these experiments ranged from 15 to 70 per cent.

The dye-hematocrit estimate of blood volume, however, showed a variable overestimate which was related to the venous cell percentage. At low venous hematocrit levels the overestimate was only 2 or 3 per cent but it increased with the venous hematocrit, being equal to the underestimate with ^{32}P at venous hematocrit levels of 50 per cent. When the latter was raised to 70 per cent by exposure to low oxygen or by infusion of concentrated red cell suspensions, the dye-hematocrit method gave an estimate of blood volume 30 per cent higher than the measured volume. These relations between the venous hematocrit and the errors in estimating blood volume with the dye-hematocrit and ^{32}P-hematocrit methods are diagrammatically shown in Figure 2.[19]

The differences shown do not, however,

preclude calculation of the correct blood volume from either of the methods *if the ratio* $\left(\frac{\text{over-all cell } \%}{\text{venous cell } \%}\right)$ *is a constant.* The venous cell percentage used in the calculations (see formulas

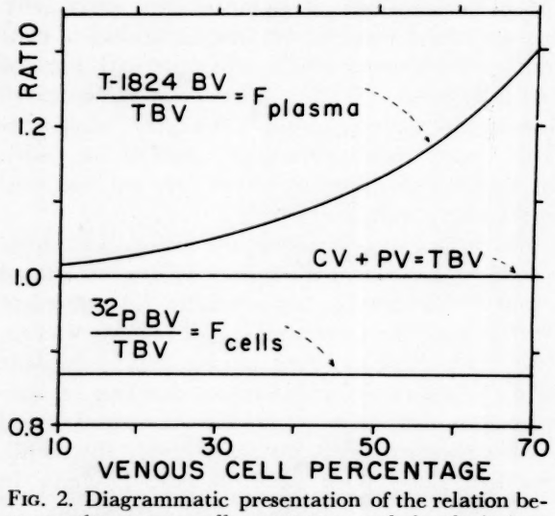


FIG. 2. Diagrammatic presentation of the relation between the venous cell percentage and the deviations of the T-1824 blood volume and of the ^{32}P blood volume estimates from the true blood volume, when the ratio

$$\frac{\text{over-all cell percentage}}{\text{venous cell percentage}}$$

is 0.87 (F_{cells} value in the splenectomized dog) and assumed to be constant. (Reprinted from Reeve, Gregersen, Allen, Sear and Walcott[19] with permission from the *Am. J. Physiology.*)

A and B) need only be multiplied by the factor, F_{cells}, representing this ratio. The equations may then be rewritten

$$\frac{PV \times 100}{100 - HF_{cells}} = BV$$

$$\frac{CV \times 100}{HF_{cells}} = BV$$

in which H stands for the venous cell percentage, PV the measured plasma volume and CV the measured cell volume.

It must be emphasized however that the ratio F_{cells} may not be a constant under all conditions. To be sure, in the splenectomized dog under the experimental conditions already considered the average value was 0.87, showing little variation except, as noted, in dogs that were infused with large volumes of dextran immediately after severe hemorrhage, but the problem clearly deserves further exploration. In man (adults) the average F_{cells} value appears[12,21] to be 0.91 but is somewhat lower in infants.[22] In the rabbit[13] the F_{cells} value is 0.85 and in the monkey the present writer has found the average to be approximately 0.81, with indications of a marked reduction during radiation sickness.

Where is the "extra plasma"? It appears from the results previously discussed that in the splenectomized dog the plasma volume exceeds by about 13 per cent the amount required to contain the red cells if these were distributed with plasma in the proportion existing in the venous blood. Where is this pool of "extra plasma"?

Microscopic observations on blood flowing through capillaries and small vessels indicate that the blood in this region has a lower ratio of cells to plasma than that in large vessels, and Fahreus[23] demonstrated this to be true also of blood flowing through tubes of small diameter. Ebert and Stead's[24] observations provide additional evidence. This, however, does not prove that all the "extra plasma" is located in the small vessels and capillaries. There may or may not be enough blood in this part of the vascular bed to account for the "extra plasma." Bazett[25] estimated that small vessels hold at most only 15 per cent of the blood and if all the extra plasma is in this region the blood there must be practically cell-free.

Allen and Reeve[26] have attempted direct analysis of the amounts of cell and plasma in freshly excised spleen, liver and kidney tissue in dogs. The cell percentage in the blood in these tissues was compared with that in samples of blood drawn simultaneously from large vessels (venous). In spleen blood the cell percentage was on the average 1.7 times that in the venous blood; in liver 0.7, and in kidney 0.5. The difference between liver and kidney is interesting in view of the double capillary bed in the latter. Furthermore, the liver and kidney together contained nearly 24 per cent of the animals' measured blood volume, and approximately 60 per cent of the total "extra plasma."

Another approach to the distribution of "extra plasma" was made by studies on the eviscerate dog.[27] In this preparation the proportion of "extra plasma" was not significantly different from that in the normal splenectomized dog. In conjunction with the results from the analyses of liver and kidney this evidence makes it seem highly improbable that "extra plasma" is present as a localized pool in some tissue or

organ but rather that it is uniformly distributed in the various branches of the vascular tree.

We have noted that in the splenectomized dog the ratio $\frac{\text{over-all cell } \%}{\text{venous cell } \%}$ (F_{cells}) is relatively constant despite large alterations in blood volume which presumably affect profoundly the circulation through small vessels. If we assume that all the extra plasma is contained in the small vessels and capillaries then, from the evidence, we are driven to the rather unexpected conclusion that the volume of blood in the capillaries is a constant fraction of the total blood volume.[27]

REFERENCES

1. Gregersen, M. I. Blood volume. *Ann. Rev. Physiol.*, 13: 397, 1951.
2. Nickerson, J. L., Sear, H. and Reeve, E. B. Simultaneous measurements of cell volume with ^{55}Fe and ^{32}P in splenectomized dogs. *Am. J. Physiol.*, vol. 175, November, 1953.
3. Gregersen, M. I., Boyden, A. A. and Allison, J. B. Direct comparison in dogs of plasma volume measured with T-1824 and with antigens. *Am. J. Physiol.*, 163: 517, 1950.
4. Sear, H., Allen, T. H. and Gregersen, M. I. Simultaneous measurement in dogs of plasma volume with ^{131}I-human albumin and T-1824 with comparisons of their long term disappearance from the plasma. *Am. J. Physiol.*, vol. 175, November, 1953.
5. Allen, T. H., Pallavicini, C. and Gregersen, M. I. Simultaneous measurement of plasma volume with hemoglobin and with T-1824. *Am. J. Physiol.*, vol. 175, November, 1953.
6. Hevesy, G., Köster, K. H., Sørenson, G., Warburg, E. and Zerahn K. The red corpuscle content of the circulating blood determined by labelling the erythrocytes with radio-phosphorus. *Acta med. Scandinav.*, 116: 561, 1944.
7. Reeve, E. B. and Veall, N. A simplified method for the determination of circulating red cell volume with radioactive phosphorus. *J. Physiol.*, 108: 12, 1949.
8. Nachman, H. M., James, G. W., Moore, J. W. and Evans, E. I. A comparative study of red cell volumes in human subjects with radioactive phosphorus tagged red cells and T-1824 dye. *J. Clin. Investigation*, 29: 258, 1950.
9. Berson, S. and Yalow, R. The use of K^{42} or P^{32} labeled erythrocytes and I^{131} tagged human serum in simultaneous blood volume determinations. *J. Clin. Investigation*, 31: 572, 1952.
10. Gibson, J. G., Peacock, W. C., Seligman, A. M. and Sack, T. Circulating red cell volume measured simultaneously by the radioactive iron and dye methods. *J. Clin. Investigation*, 25: 838, 1946.
11. Barnes, D. W. H., Loutit, J. F. and Reeve, E. B. A comparison of estimates of circulating red blood cell volume given by the Ashby marked red cell method and the T-1824 hematocrit method in man. *Clin. Sc.*, 7: 135, 1948.
12. Reeve, E. B. Use of radioactive phosphorus for the measurement of red-cell and blood volume. *Brit. M. Bull.*, 8: 181, 1952.
13. Armin, J., Grant, R. T., Pels, H. and Reeve, E. B. The plasma, cell and blood volumes of albino rabbits as estimated by the dye (T-1824) and ^{32}P marked cell methods. *J. Physiol.*, 116: 59, 1952.
14. Schambye, P. Det cirkulerende blodvolumen hos får bestemt med P^{32} maerkede erytrocyter og T-1824. *Nord. veterinar-medicin*, 4: 929, 1952.
15. Gregersen, M. I. Unpublished observations.
16. Hahn, P. F., Bale, W. F., Ross, J. F., Balfour, W. M. and Whipple, G. H. Red cell and plasma volumes (circulating and total) as determined by radio-iron and by dye. *J. Exper. Med.*, 75: 221, 1942.
17. Nickerson, J. L., Sharpe, L. M., Root, W. S., Fleming, T. C. and Gregersen, M. I. Simultaneous blood volume determinations in dogs with dye (T-1824) carbon monoxide and radioactive iron Fe^{55}. *Federation Proc.*, 9: 94, 1950.
18. Reeve, E. B., Gregersen, M. I., Allen, T. H. and Sear, H. Distribution of cells and plasma in the normal and splenectomized dog and its influence on blood volume estimates with P^{32} and T-1824. *Am. J. Physiol.*, vol. 175, November, 1953.
19. Reeve, E. B., Gregersen, M. I., Allen, T. H., Sear, H. and Walcott, W. W. Effects of alteration in blood volume and venous hematocrit in splenectomized dogs in the estimates of total blood volume with ^{32}P and T-1824. *Am. J. Physiol.*, vol. 175, November 1953
20. Root, W. S., Allen, T. H. and Gregersen, M. I. Simultaneous determinations in splenectomized dogs of cell volume with CO and ^{32}P and plasma volume with T-1824. *Am. J. Physiol.*, vol. 175, November, 1953.
21. Gray, S. J. and Frank, H. The simultaneous determination of red cell mass and plasma volume in man with radio-active sodium chromate and chromic chloride. *J. Clin. Investigation*, 32: 1000, 1953.
22. Mollison, P., Veall, N. and Cutbush, M. Red cell and plasma volume in newborn infants. *Arch. Dis. Childhood*, 25: 242, 1950.
23. Fahraeus, R. The suspension stability of the blood. *Physiol. Rev.*, 9: 241, 1929.
24. Ebert, R. V. and Stead, E. A., Jr. Demonstration that the cell plasma ratio of blood contained in minute vessels is lower than that of venous blood. *J. Clin. Investigation*, 20: 317, 1941.
25. Bazett, H. C. *Macleod's Physiology in Modern Medicine*, 9th ed., p. 341. St. Louis, Mo. C. V. Mosby Company.
26. Allen, T. H. and Reeve, E. B. Distribution of "extra plasma" in the blood of some tissues in the dog as measured with ^{32}P and T-1824. *Am. J. Physiol.*, vol. 175, November, 1953.
27. Gregersen, M. I., Cizek, L. J. and Allen, T. H. The proportion of "extra plasma" in the eviscerate dog. *Am. J. Physiol.*, vol. 175, November, 1953.

Combined Staff Clinic

Malabsorption Syndrome

THESE are stenotyped reports of Combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Gilbert H. Mudge.

DR. RICHARD J. CROSS. The living organism is capable of many accomplishments which are beyond the comprehension of man today. One of these is the efficient way in which those elements of food which are of nutritive value are absorbed from the intestinal tract, frequently against a considerable concentration gradient. In this Clinic we shall consider disorders of this function and some of the diseases which result therefrom. A discussion of these abnormalities can profitably be started with a review of normal intestinal absorption, and to provide this we have a distinguished visitor, Dr. Stetten, from the Public Health Research Institute of the City of New York.

DR. DEWITT STETTEN, JR.: I should like, in a few sentences, to refresh your memories on the mechanisms of absorption of fats from the gastrointestinal canal. You will recall that one important event which apparently must precede the absorption or digestion of fats is emulsification. This process is favored in the intestinal lumen by the presence of the salts of bile acids which are of themselves excellent detergents. Also contributing to this emulsification are the products of digestion of fat, including the lower glycerides, the mono- and diglycerides, and perhaps the soaps which are formed from such digestion.

There is at least one very potent lipolytic enzyme in the pancreatic juice, pancreatic steapsin or lipase. Mention also has been made in the literature of a gastric lipase, of very questionable significance in the adult but of possible significance in infancy, and of the presence of lipases in the succus entericus, as well as lipases of bacterial origin. Little is known about the role of these latter lipases in man.

In addition to its role in emulsifying fat prior to digestion, bile salt plays an as yet unidentified role in the transport of the products of digestion of fat across the intestinal barrier. At one time this action of bile salt seemed clarified when it was discovered by Windaus that bile acids form water-soluble conjugates with many water-insoluble materials. However, recent reviewers, especially Verzar, are inclined to reject formation of such "choleic acids" as playing an important part in the absorption of fats.

Historically, there appear to be two conflicting theories which have confused the literature over the last fifty or seventy-five years. The first of these may be termed the "lipolytic theory" which was originated by Pflüger in the latter half of the nineteenth century. This supposed that fat was completely hydrolyzed and that the products of hydrolysis were absorbed. A second, contrasting view is the so-called "partition theory" advocated by Frazer, who would have it that fat may be partially digested, partially hydrolyzed, and that that portion of fat which is hydrolyzed to fatty acid is absorbed predominantly by the portal route and comes to the liver as free fatty acid. The remainder, which is unhydrolyzed, is absorbed predominantly by the chylous route and enters the blood stream at the venous angle of the neck.

In considering the evidence relating to these two theories, we may revert to the observations of Munk, published in Virchow's Archiv in 1891. It is surprising how much of our present day information comes from this one paper. Munk is apparently less well known than Beaumont although what he did is rather similar. He had the good fortune to encounter a patient with a chyle fistula and he abused this patient much as Alexis St. Martin was abused, although in this case we do not know the name of the patient. I should like to read you a brief passage from this rather ponderous paper.

"In August 1889, a Russian-Polish, well-developed 18-year old girl entered the surgical department of our local hospital. Elephantiasis had developed four years earlier, progressing from above downwards in the left leg. . . On the upper half of the inner surface of the thigh,

near the end of the upper third of the lower leg, a small fistulous opening was found on the posterior or flexor side, out of which a milky fluid trickled."

Munk subjected this lady to many tests, and he observed that when she was fasting the fluid discharged from the fistula was clear whereas immediately or shortly after meals the fluid became milky. He did fat analyses, both on fasting lymph and on postprandial chyle, and found that in the fasting fluid there was practically no fat, values as low as 0.6 per cent being found. After ingestion of a high fat meal, however, the fat content of this fluid would rise to approximately 5 per cent, which is reasonably heavy cream.

He fed various fats to this patient and found that he could recover, within the succeeding twelve or thirteen hours, between 60 and 66 per cent of the ingested fat—this quite consistently. The fat which he recovered was mostly neutral fat, although it contained some 7 per cent of phosphatides, some 3 per cent of cholesterol. He further showed that the fat which he was recovering from the chyle was indeed the fat which he had previously fed to the patient. Thus in a primitive labeling experiment when olive oil was fed, the fat recovered from the chyle was liquid at room temperature; when mutton fat was fed, the fat recovered from the chyle was solid at room temperature.

He made one other curious observation, namely, that while the fistula was open and flowing there was no lipemia following the ingestion of a high fat meal; but when, incident to treatment, the fistulous tract closed, there was a very considerable lipemia following the ingestion of a fatty meal. From these observations he concluded that virtually all the fat which was absorbed entered the body by the lymphatic route, and this observation is, I think, today well substantiated.

Despite the claims of opponents, the route of chylous absorption has been supported strongly by observations of recent years in several laboratories, notably those of Bollman, Chaikoff and Bergstrom. These investigators all have found that in excess of 90 and often in excess of 95 per cent of the fat which leaves the intestinal canal can be recovered from the chyle, provided the surgical procedure for collecting chyle is adequate. This was true whether the material fed was free fatty acid or triglyceride, which of itself would appear to invalidate the partition theory of Frazer as it was originally proposed. There is, however, a partition, and this partition relates not to whether the fatty acid is esterified or free, but rather to the chain length of the fatty acid. Thus in studies by Bloom in Chaikoff's laboratory it was shown that whereas virtually all the palmitic or stearic acid fed, containing 16 or 18 carbon atoms, could be recovered in the chyle, only 60 to 80 per cent of the 14-carbon myristic acid, 15 to 50 per cent of the 12-carbon lauric acid and less than 20 per cent of the 10-carbon decanoic acid that was absorbed could be accounted for in the chyle. From this it has been concluded that fatty acids of 10-carbon atoms or less are probably absorbed chiefly by the portal route whereas the longer-chain fatty acids which, of course, make up the bulk of the dietary fatty acids, are absorbed by the lymphatic route.

The next question relates to the extent of lipolysis which precedes absorption. This is a difficult question to study and is made particularly difficult by observations both in our laboratory and some published observations from Bergstrom's laboratory, that the lipolytic reaction is reversible in the intestinal tract. If one feeds labeled fatty acid together with unlabeled glyceride and, from the intestinal tract, recovers the glyceride fraction, one finds labeled fatty acid esterified to glycerol. This is certainly not surprising but it does confuse any attempt to analyze the degree of hydrolysis of fat which must precede absorption.

Studies from Reiser's laboratory within the last two years have indicated that complete hydrolysis is not necessary for absorption; that probably a large portion of the fat which is absorbed has been hydrolyzed down to the monoglyceride level, but no further. Similar results by Bloom and Chaikoff have indicated that the phospholipids of the cephalin and lecithin variety also need not be completely hydrolyzed prior to absorption. It must be understood that regardless of the degree of hydrolysis prior to absorption, resynthesis of neutral fat does occur, and what one finds in the chyle is chiefly triglyceride.

The question of how these materials actually pass the mucosal barrier also is not satisfactorily answered today. That emulsification has something to do with it is clear since highly emulsified preparations of such chemically inert materials as paraffin will cross the intestinal barrier if the emulsification is sufficiently fine. There is, then,

some degree of purely physical passage of droplets across the mucosa, if these are sufficiently small. However, for many years Verzar and his school have argued that the absorption of fat is more than mere physical passage and involves an active process operating in the mucosal cells. Evidence for this stems from the observation that such poisons as phlorhizin, which is supposed to poison phosphatase, or iodoacetic acid, which is an inhibitor of glycolysis, will markedly inhibit the passage of fatty materials across the intestinal barrier.

Precisely what happens at the mucosal cell is, I think, not known. It was suggested years ago that the phospholipids of the mucosal cells turned over very rapidly and that this turnover was responsible for the delivery of fatty acids from one border to the other of the mucosal cell. Sinclair advocated this view strongly, and some supporting evidence was found by Artom and his collaborators who measured the rate of phospholipid turnover in intestinal mucosa during fasting and after the ingestion of a fatty meal. They found some increase in turnover of phospholipids in the absorptive state. These findings, however, have not been confirmed in Chaikoff's laboratory and consequently the role of the phospholipids in the absorption of fat is today an open question.

It should be pointed out that the absorption of fat is subject, directly or indirectly, to a variety of controls. As early as 1934 it was reported that the adrenalectomized animal absorbs fat from the intestinal lumen far less efficiently than does the normal animal, and that addition of the adrenal steroids then available, mixed adrenal materials, could restore the absorption of fat to normal levels. Similarly, hyperthyroidism appears to interfere with the absorption of fat. It is not intended to suggest that these are direct consequences of the endocrines involved. The animals are very sick and the observed effects may indeed be very indirect consequences of the primary endocrine disturbances.

It has been pointed out that iodoacetate does interfere with fat absorption, and a sprue-like syndrome may be produced in experimental animals by the oral administration of iodoacetic acid. Whether this bears any relationship to the steatorrhea of clinical sprue is a matter for subsequent argument and experiment.

Before concluding, I should like to say something about the absorption of sugars. You will recall that of the dietary hexoses of importance, galactose, glucose and fructose are actively absorbed across the intestinal barrier, and in that sequence—galactose > glucose > fructose. The hexokinase of intestinal mucosa attacks these three sugars also and apparently in the same relative rate; that is, galactose is phosphorylated by intestinal mucosal hexokinase more rapidly than is glucose which is, in turn, phosphorylated more rapidly than is fructose. Furthermore, it has been shown that when glucose is being absorbed, glucose phosphates are demonstrable in the cells of the intestinal mucosa; when galactose is being absorbed, galactose phosphates are demonstrable in these cells. This again suggests that phosphorylation is in some wise associated with the active absorption of sugar.

The defect in sprue I should prefer to leave for later discussers. But it should be pointed out that the defect is apparently a fairly specific one, in view of the reported finding that whereas the absorption of glucose from the intestinal tract may be markedly inhibited, as indicated by a flat oral glucose tolerance curve, the absorption of fructose, it has been claimed, is normal in this disease. This means that even though the two sugars are probably absorbed by very similar mechanisms, the disease entity, sprue, dissects apart these two mechanisms, interfering with one and not with the other absorptive process.

DR. CROSS: As Dr. Stetten has pointed out, because of their insolubility in aqueous solutions fats are hard to absorb, and it is hardly surprising that difficulties which patients have with intestinal absorption are apt to be characterized by excessive amounts of fat in the stool, otherwise known as steatorrhea. The classification of these steatorrheas can be a complicated and confusing thing, but I think if we stick to what Dr. Stetten has told us an orderly classification is possible. An attempt in that direction is shown in Table 1.

It is well known that moderate steatorrhea is common in jaundiced patients, presumably because of poor emulsification of fat in the absence of bile salts. The loss of fat is not great in this condition, however, whereas absence of pancreatic secretions is apt to give rise to very severe steatorrhea, presumably because of lack of lipase and poor emulsification. The small intestine of these patients may contain a large amount of neutral fat but the fecal fat is often largely hydrolyzed, presumably through the action of

bacterial lipases. For this reason the presence of fatty acids in the stool in no way excludes pancreatic disease as a cause of the steatorrhea. Such exclusion can best be accomplished through demonstration of normal pancreatic enzymes in the duodenal contents. A simpler but somewhat less reliable test is analysis of the feces for nitrogen. In cases of pancreatic steatorrhea there is, in general, a high fecal nitrogen, probably because of inadequate digestion of proteins. Also included in this general group are the steatorrheas which are encountered after partial or total gastrectomy although the mechanism is not at all clear.

TABLE 1

CLASSIFICATION OF THE STEATORRHEAS

1. Defects in digestion and/or emulsification
   (a) Hepatic—obstructive jaundice, hepatitis
   (b) Pancreatic—cystic fibrosis, chronic pancreatitis, after pancreatectomy
   (c) Gastric—after gastrectomy
2. Lack of small intestine
   (a) After resection
   (b) Fistulas
3. Defects in absorption, mechanism obscure
   (a) Celiac disease
   (b) Sprue
4. Diseases involving intestinal wall
   (a) Regional enteritis
   (b) Scleroderma
   (c) Amyloid
5. Diseases of intestinal lymphatics
   (a) Tuberculosis
   (b) Hodgkin's disease
   (c) Intestinal lipodystrophy
6. Rapid transit
   Moderate steatorrhea may be associated with diarrhea of any cause

Difficulties in fat absorption obviously may be anticipated when a large part of the small intestine has been eliminated, either by the surgeon's knife or by a short-circuiting fistula. In the latter instance other factors may be present, such as intestinal stasis and abnormal bacterial growth, which may contribute to the steatorrhea.

The third group is made up of the so-called idiopathic steatorrheas, which include the great majority of patients with steatorrhea severe enough to be of clinical importance. These will be discussed in detail by other speakers.

In the light of what Dr. Stetten has said, absorption of fat may be interfered with in diseases involving either the intestinal wall or the intestinal lymphatics, and in Table 1 some of these diseases are listed. The title of the sixth category may be misleading because it almost certainly represents a considerable oversimplification. For in diarrhea of any cause there are probably abnormalities of the small intestine, whether or not these are evident to the pathologist, and these abnormalities may have more to do with causing steatorrhea than does the shortened transit time.

The commonest and most interesting causes of steatorrhea are those in Group 3—sprue and celiac disease—and we are going to concentrate on these for the rest of the clinic. We are fortunate in having in this institution experts who have devoted many years to a careful study of these conditions. The next speaker is one of these, Dr. di Sant'Agnese, who will tell us a little about the life history of these diseases and the relationship between them.

DR. PAUL DI SANT'AGNESE: In 1889 Gee described a chronic nutritional disturbance of children and adults characterized by marked malnutrition, abdominal distention and diarrhea with large, pale, foul-smelling stools containing an excess of fat. A distinction was subsequently made between the disease in children, celiac disease (from the Greek word, κοιλία, meaning abdomen) and that of adults, sprue (from the Dutch word, *sprouw*, meaning aphthous stomatitis).

The remarks we shall make today will be limited to idiopathic celiac disease and primary or idiopathic non-tropical sprue. It is our belief that these two conditions are not two separate diseases but merely the expression of the same basic disturbance at different ages. This was first recognized by Gee in the original description of the disease and reaffirmed by Thaysen[1] in Denmark and Hanes in this country, among others. For simplicity, we shall refer to this condition as childhood and adult celiac disease.

Idiopathic celiac disease is characterized by chronic or recurrent diarrhea without demonstrable anatomic or bacteriologic basis, great loss of weight, flatulence, intolerance to dietary fat, greater than normal requirement for dietary protein and, in children, marked intolerance to dietary starch. It is marked by progressive malnutrition, steatorrhea, hypoproteinemia, hydrolability and the development of a deficiency state with multiple vitamin and mineral deficiencies. Tetany, edema, osteoporosis, osteomalacia and, at times, rickets may be present. On roentgenographic examination of the small intestine, evidences of abnormal

motility are seen, with clumping, segmentation, and flocculation of barium, hypotonicity of intestinal loops and an increased intestinal transport time; the so-called "deficiency pattern" of Golden and Lepore.[2] In the fully developed clinical picture there is evidence of impaired fat and carbohydrate absorption as indicated by a flat vitamin A and glucose tolerance test and an increase in fecal fat and, at times, in fecal starch. The fecal nitrogen is normal except during periods of acute diarrhea. The stools are bulky, greasy and foul.

There frequently is anemia, usually of a microcytic hypochromic variety in children, and of a macrocytic hypochromic or normochromic type in adults. Gastric acidity may be reduced in all age groups and may even be absent in adults.

Past observers have viewed the disease either as idiopathic steatorrhea, with the essential defect in fat absorption, or as a result of chronic infection. While the etiology of celiac disease is still not clearly known, evidence has been accumulating[3] that there is a hereditary constitutional defect in metabolism which persists after the clinical manifestations of the severe illness have disappeared. This defect is transmitted as a dominant trait of variable penetrance and expressivity. Its true nature has not yet been revealed by chemical, bacteriologic or postmortem investigations.

The basic defect (Table II) may manifest itself at different ages, either because of inherent differences in the severity of the disease itself or because of the occurrence of appropriate extrinsic conditions. It may also remain mild or latent for an indefinite period of time and manifest itself at times later in life, when appropriate trigger mechanisms are set off. Trigger mechanisms are varied and may consist of acute enteral or parenteral infections, dietary deficiency, administration of a wide spectrum antibiotic, or often psychic trauma. The same defect may lead to different but comparable disease pictures at different ages and under different conditions. Among these are celiac disease, so-called primary idiopathic non-tropical sprue, and probably a variety of other milder gastrointestinal disturbances.

Three lines of argument may be cited in support of the theory that impaired intestinal fat absorption is not the only or perhaps even the most important physiologic disturbance in this disease, although clinically it is the manifestation which has attracted most attention in the past.

First, evidence has been accumulated by Dr. Dorothy Andersen that for each severe case of celiac disease with steatorrhea in children, there are several, at times in the same families, with a similar but milder clinical picture and without an increase in fecal fat. When a child improves the steatorrhea disappears, even though the patient is not cured by either clinical or laboratory criteria and an increased fecal fat is apt to reappear if there is recurrence of severe disease. Dr. Lepore and I have reason to believe that a somewhat similar sequence of events may obtain in adults.

Second, it is the accepted experience that children and adult celiacs have severe symptoms when only as much as 70 to 80 per cent of the fat intake is absorbed. When compared with a fat absorption of 50 per cent or less in almost symptom-free cases with pancreatic deficiency, it does seem as if other factors must be important in the etiology of the disease.

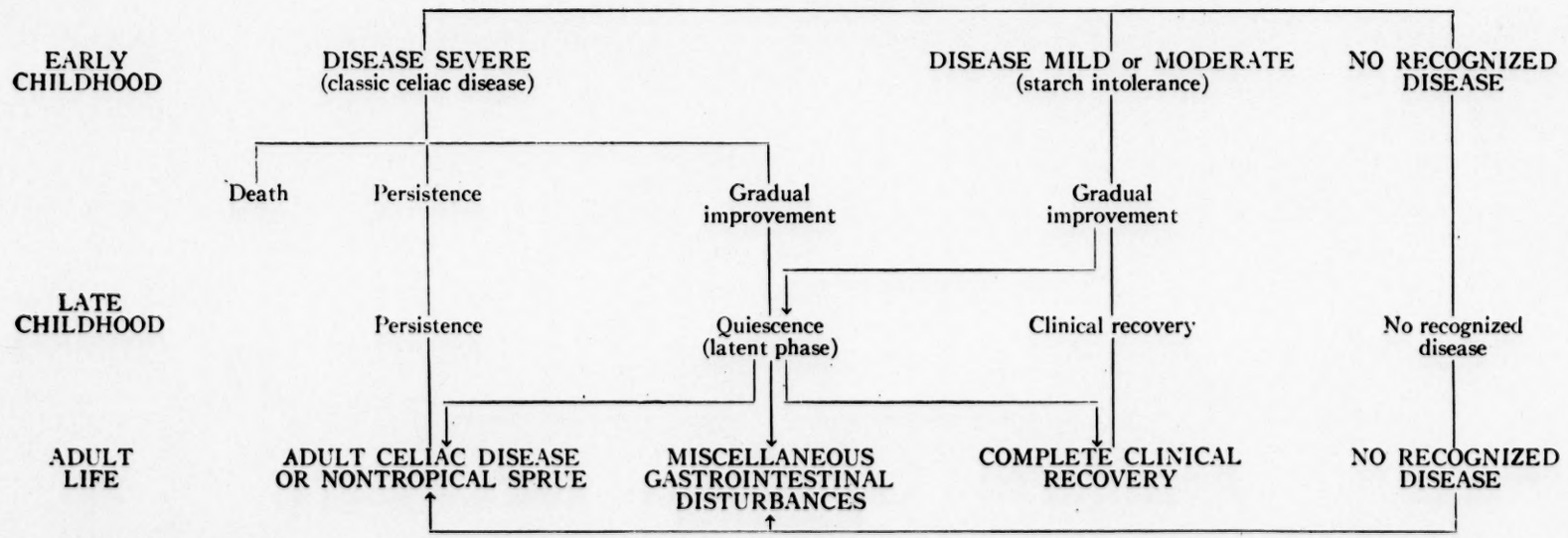
Third, despite a normal fecal nitrogen and high protein dietary intake the disease is marked by hypoproteinemia. Is there something wrong with the way nitrogen is metabolized or is there something wrong with the absorption of specific amino acids?

The familial occurrence of celiac disease, stressed first by Andersen and confirmed by Ebbs in Toronto, is a strong argument in favor of the existence of a basic hereditary constitutional defect. According to this concept, enteral or parenteral infections which, especially in children, commonly initiate the manifest disease, act as trigger mechanisms precipitating a symptom-complex which might otherwise have remained latent or unrecognized. They therefore play a secondary and not a primary role in the etiology of celiac disease.

Allergy has been repeatedly advanced as an etiologic factor but the part it plays must be small. In a series of eighty-one patients at the Babies Hospital the incidence of allergy was found not to be significantly different from that of the general population. It is possible, however, for gastrointestinal allergy to produce symptoms simulating celiac disease. Interesting in this connection is the recent observation of Dicke in Holland on the adverse effect of wheat gluten, but not of deproteinized wheat polysaccharide, on intestinal fat absorption in children with celiac disease. This observation has

TABLE II*

BASIC CONSTITUTIONAL METABOLIC DEFECT
(usually insidious onset)



* The natural history of celiac disease. (From ANDERSEN, D. H. and DI SANT'AGNESE, P. A. The Celiac Syndrome. In Brennemann's Practice of Pediatrics, vol. 1, chap. 29. W. F. Prior Co.)

been confirmed by Wejers and van de Kamer in Holland and Sheldon in London in children and has been extended to adults by Frazer in Birmingham. We do not think, however, that sensitivity to feeding of gluten explains the whole problem of celiac disease but that it should be regarded as one of the trigger mechanisms that may bring out an underlying constitutional defect.

No figures are available as to over-all incidence but the disease is being recognized with increasing frequency. Traditional descriptions refer only to the advanced cases of the disease. In the severe form it is not very common but in mild form it is widespread in children and perhaps in adults. Celiac disease occurs in the white race regardless of national origin. It seems to be uncommon among Negroes and has never been reported, to my knowledge, in Orientals.

The differential diagnosis of idiopathic celiac disease is not too difficult in patients with long-standing symptoms who have developed all the classical manifestations of the celiac state. A difficult diagnostic problem is posed, however, by those who, because of their early age or the short duration of the disease, have not yet developed the whole constellation of symptoms traditionally expected of a celiac patient. It should be stressed that no single laboratory test is pathognomonic of idiopathic celiac disease and diagnosis should be based on the clinical and laboratory picture as a whole and not on the presence or absence of single factors. Until the true nature of the basic defect is better understood, exclusion of other conditions presenting similar clinical pictures and, perhaps, response to dietary and other therapy will be important. Laboratory work-up may have to include culture of the stools, examination of the stools for ova and parasites, serum carotene levels, glucose tolerance test, roentgenographic examination of the intestinal tract and, certainly in children, duodenal drainage for pancreatic enzymes.

I should like now to present very briefly some observations bearing on the natural history of idiopathic celiac disease, on the identity of the childhood and adult forms of the disease, and on some of the differences between the symptomatology of non-tropical sprue as it is seen nowadays and its traditional descriptions.

Celiac disease is most frequently encountered in subjects below the age of five years or above the age of twenty-five years. It has always been something of a mystery as to what happens in between. Some observations on the subject were published in 1939 by Hardwick in England and more recently by Zellweger and Lauchli in Switzerland, but the information at hand was meager and we decided to investigate the problem further.

I was privileged to study, three to eleven years after the original admission, a group of twenty-three children ranging in age from five to thirteen years who had been thoroughly investigated by Dr. Dorothy Andersen in the acute phase of celiac disease in early childhood.[4,5] All these patients were clinically well; they were following an essentially normal diet with no additional medication with the exception of vitamin supplements, and they were taking part in all activities appropriate to their ages. There was some voluntary restriction of dietary fat but starch intake was not greatly decreased in most instances. A few were on the small side of normal but growth and development had not been seriously impaired.

These patients were readmitted to the Babies Hospital for study which included blood determinations, vitamin A and glucose tolerance curves, duodenal drainage, chemical determination of fecal fat and roentgenographic examination of the intestinal tract. Much to our surprise we found that many of the chemical tests, especially those relating to intestinal fat absorption, still indicated impairment of function despite the absence of clinical symptoms. This period in late childhood, which is characterized by the persistence of abnormal laboratory findings despite complete or almost complete clinical recovery, evidently represents a latent phase of celiac disease.

Two conclusions can be drawn from these observations: First, intolerance to dietary starch, which is an outstanding and at times predominant symptom in young children, becomes less marked after the age of three or four. Conversely, impairment of fat absorption and intolerance to dietary fat plays an increasingly important role in the diagnosis and treatment of celiac disease in older children.

Second, the persistence of abnormal laboratory findings after years of clinical improvement or even apparent recovery supports the hypothesis that there is a basic constitutional defect in celiac disease. It also seems logical to expect that some of the patients who have had severe celiac disease in childhood may develop gastrointestinal disturbances in adult life.

We were then faced with the prospect of following these patients for the next thirty or forty years in order to study their clinical behavior; but being impatient by nature we decided to do the next best thing and study a group of ten adult patients with idiopathic non-tropical sprue.[6] All patients had severe diarrhea, flatulence and weight loss. Surprisingly, only two of ten had tetany, two others occasional edema and three a very moderate degree of stomatitis; thus in seven of ten cases the stomatitis, from which the name of sprue is derived, was absent. All of the patients had marked steatorrhea, flat glucose and vitamin A absorption curves and a disturbed small intestinal motility on roentgenographic examination. There was a variable degree of hypoproteinemia. All cases had absent carotene in the serum but the vitamin A levels in the serum were normal in every instance.

In six of ten cases there was either a family incidence of celiac disease or a history of the onset of the disease in childhood. In two of these patients both of these findings were present. For example, in J. M., a white male, idiopathic non-tropical sprue first became apparent at the age of twenty-seven years. Two of his children were admitted in early childhood to the Babies Hospital with severe celiac disease. In H. M., a white female, symptoms first appeared at the age of six months. She was admitted to Babies Hospital with typical clinical and laboratory findings and a diagnosis of celiac disease was made. She was placed on an appropriate regimen and appeared to recover completely from her illness but at the age of twenty-five years, following psychic trauma, she was admitted to Presbyterian Hospital with all of the classical manifestations of idiopathic non-tropical sprue.

It is worth while to mention the usefulness of low or absent serum carotene levels as a non-specific indication of the presence of steatorrhea. Serum carotene levels are abnormally low in any condition which gives rise to increased fecal fat, whatever the etiology may be: idiopathic celiac disease, cystic fibrosis of the pancreas, total pancreatectomy, post-gastrectomy syndrome, etc. On the other hand, single serum levels of vitamin A have little significance because they frequently reflect the preformed vitamin A which has been fed in the form of vitamin supplements in the few days preceding the test.

The clinical and laboratory picture of celiac disease in children and adults therefore is essentially the same. Many of the clinical features traditionally expected in adult sprue and usually lacking in the childhood disease, such as stomatitis, are no longer commonly found. Perhaps they were an expression of a deficiency state, partly overcome by the widespread administration of vitamins and the better dietary conditions prevalent nowadays.

The type of anemia remains a difference between the two age groups. It is usually of the microcytic hypochromic variety in children and of the macrocytic hypochromic or normochromic type in adults. Evidence is being gathered that the bone marrow may respond differently to the same deficiency at various age levels or that different deficiencies are apt to develop in different age groups.[5]

Another difference between child and adult celiacs is the so-called "celiac crisis," an acute episode of dehydration and acidosis. Such crises are seen chiefly in children less than two years of age, in whom normally there is marked instability of water and electrolyte balance. Two of the adult patients with non-tropical sprue whom Dr. Lepore and I observed on the wards of the Presbyterian Hospital had a similar episode, with vomiting, watery diarrhea and dehydration, but life was not as rapidly endangered as in the case of infants.

Even if idiopathic celiac disease and idiopathic non-tropical sprue are considered to be the same condition in two different age groups, it must be recognized that most of the laboratory tests (e.g., flat glucose tolerance curves, steatorrhea, abnormal small intestinal motility on roentgenographic examination, etc.) are much more consistently found in adults than in children. This difference, however, may be satisfactorily accounted for by the irreversible changes which take place in intestinal function due to age and long-standing disease.

Before concluding, something should be said about the relation between so-called idiopathic non-tropical sprue and the disease that first manifests itself in the tropics. If a patient with the basic constitutional defect in whom celiac disease has remained latent goes to the tropics, it is to be expected that the condition will become clinically overt following a period of dietary deficiency or an enteric infection. Both are good trigger mechanisms. This type of sprue, which we have observed in two missionary families, is no different from the idiopathic non-tropical variety. On the other hand, many con-

ditions undoubtedly occur in tropical climates which may give rise to a syndrome similar to sprue but frequently transitory in nature. This should be considered a secondary, not a primary form of sprue.

DR. CROSS: We shall now devote a few minutes to some of the difficulties with electrolytes which patients get into when they have steatorrhea. Dr. Plimpton is going to cover this phase of the problem for us.

DR. CALVIN H. PLIMPTON: In the malabsorption syndrome, and especially in sprue, the more usual manifestations of electrolyte disturbance tend to reflect calcium rather than sodium and potassium loss. Because of a low serum calcium, patients with sprue may present paresthesias, muscle cramps and even frank tetany. The phosphorus in the serum is also frequently low, with the result that the bones are poorly mineralized to the point of osteomalacia. These soft bones can give pain and may fracture.

As Dr. di Sant'Agnese indicated, a low serum calcium is found in some cases of sprue. When the serum calcium is low there is usually an increased amount of calcium in the stool. The mechanism for the increased stool calcium is of interest. It is probably not due to increased excretion of calcium in the intestinal juices. If a large amount of calcium is given to a patient with sprue, the extra calcium is all recovered in the stool and there is no rise in the urine calcium. Since the urine calcium normally represents about 15 to 30 per cent of the ingested calcium, the failure to rise would suggest that none of the extra calcium was getting into the circulation.

Intestinal hurry, or rapid transit, and decreased acidity of gastric juice have already been discussed in relation to the malabsorption syndrome, and so will be mentioned here only as minor factors. The most favored theory for the increased stool calcium has been that the presence of the extra fat in the stool either mechanically traps the calcium or else chemically binds it in the form of soaps. It is perfectly true that soaps are formed but, we think, in too small amount to explain the calcium loss. If the calcium were being mechanically trapped by the extra fat one would expect that the calcium loss would vary directly with the amount of fat loss. Clinically, we know that this is only a very crude relationship. Comfort has shown that with an intake of 45 gm. of fat and 2.5 gm. of calcium there may be 29 gm. of fat and 1.9 gm. of calcium in the stool. With an intake of 4 gm. of fat and 3 gm. of calcium there may be 14.9 gm. of fat in the stool and 2.3 gm. of calcium. With an intake of 100 gm. of fat and 2.7 gm. of calcium there may be 65 gm. of fat and only 2.0 gm. of calcium in the stool. The calcium in the stool would thus seem to bear no direct relationship to the amount of fat in the stool.

Another and more likely explanation is that vitamin D is fat-soluble and hence, because of fecal loss, not available to aid in the absorption of calcium. There is evidence in the work of Fourman and Spray that vitamin D is not well absorbed in steatorrhea. With 12,000 units of vitamin D a day by mouth they found that only 2 per cent of the ingested calcium was absorbed. When they gave the same amount of vitamin D intramuscularly there was 8 per cent retention of ingested calcium. Although these values are not as striking as one would like, they suggest that vitamin D is not being absorbed and that if it can be gotten into the system by a route other than alimentary, calcium will be absorbed in greater amounts.

The same objection, however, can be raised to this that is raised to fat. If the calcium defect were purely a lack of vitamin D, it should parallel the defect in absorption of fat. It does not, so it may be suspected that although soaps, fat and vitamin D are factors, perhaps the difficulty with calcium absorption is an independent manifestation of malabsorption, almost as distinct as the difficulties with glucose, fat and sometimes protein. Difficulties with other electrolytes are the same as in any severe diarrhea and are not as specific a phenomenon as in the case of calcium.

DR. CROSS: Thus far we have been concentrating on studies of the nature of the disease and have said relatively little about treatment. I should like now to introduce our last speaker, Dr. Lepore, who will tell us about the management of the sprue syndrome.

DR. MICHAEL J. LEPORE: I shall limit my discussion to recent advances in the treatment of sprue, with special emphasis upon the measures currently in use in this hospital.

Ever since the early description of Gee, diet therapy has been emphasized for the management of sprue but there has been some divergence of opinion regarding the details. The Andersen diet for sprue was developed here by Dr. Dorothy Andersen for use in the celiac-sprue syndrome. It consists essentially of a high protein, high caloric, moderately low fat diet, with

easily assimilable simple carbohydrates and avoidance of excessive amounts of starch. This diet has been extremely useful in the management of children with celiac disease and in adults with the same disorder. It is my belief, however, that it is often unnecessary rigidly to restrict the starch intake in adult patients, for many of them do not exhibit starch intolerance, as Dr. di Sant'Agnese has stressed. To deprive such patients of bread, potatoes, etc., would seem to be unnecessary and creates difficulties in achieving a satisfactory total caloric intake.

Recently, Frazer has suggested that wheat gluten disturbs gastrointestinal function and may be responsible for the celiac-sprue syndrome, as Dr. di Sant'Agnese mentioned. We have not had an opportunity to study this in detail. However, one of our patients with severe sprue eats little or no wheat and, despite this, has the full-blown disease. Eliminating wheat, or encouraging the intake of excessive amounts of it, has failed grossly to modify the symptoms of two of our adult patients with sprue. It is therefore our belief that wheat gluten is merely another trigger mechanism and intolerance to it is not a basic abnormality in the sprue syndrome.

Liver extract has rightfully occupied a high place among the available therapeutic agents for this disease, ever since the early observations of Bloomfield. It has been customary to recommend crude liver extract intramuscularly in sprue but it is our belief that refined liver extract is every bit as efficacious and a good deal less painful. Furthermore, since the effective material in refined liver is almost entirely vitamin B_{12}, we have not hesitated to use vitamin B_{12} rather than liver.

Much has been written regarding folic acid and the citrovorum factor in sprue and it is apparent that they are effective agents, especially in the tropical form of the disease. In view of the observations on nutritional and macrocytic anemia, we have usually recommended oral folic acid, 5 mg. three times daily, in addition to parenteral vitamin B_{12}. Our success with all of these agents in non-tropical sprue has not, however, been dramatic in controlling the gastrointestinal symptoms.

Since the malabsorption of sprue involves many vitamins and minerals, we supplement our treatment with potent B complex and multivitamin preparations. Vitamin K deficiency may occasionally lead to severe prothrombin deficiency with hemorrhage. In two cases we have had excellent and rapid responses in a matter of hours to intravenous vitamin K in the dosage of 36 mg. or 72 mg. Iron-deficiency anemia is not infrequently seen in adult sprue. One of our patients developed severe iron-deficiency anemia which failed to respond to iron given orally. This patient, a thirty-seven year old woman with intractable sprue, had a classical microcytic, hypochromic anemia, with a mean corpuscular volume of 64 μ^3. Her hemoglobin level was 6 gm. with a red count of 4.3 million. After unsuccessful oral administration of iron she was given intravenous iron in the form of feojectin® (Dr. Elmer Brown conducted this study) and had a very dramatic and sustained hematologic response.

Another group of agents useful in the treatment of sprue are the detergents, especially tween 80.® Their mode of action is obscure, for if Frazer[7] is right there is no defect of emulsification in idiopathic sprue. However, Chester Jones and associates[8] reported a dramatic therapeutic triumph with tween 80. This was in a patient with non-tropical sprue who failed to respond to standard measures until a form of tween 80 was added. This was followed by splendid weight gain and clinical remission. Dr. Jones followed this with studies of fat absorption in which he gave vitamin A, to obtain a vitamin A tolerance curve, and then with the dose of vitamin A gave a dose, 2 gm., of tween 80. He thought there were significant changes in absorption of vitamin A, attributable to tween 80. It is of interest that the major changes seem to have occurred in conditions other than sprue and were most pronounced in the post-gastrectomy state. Our own experience with tween 80, in the form of sorlate,® has been disappointing.

Despite the many available therapeutic agents, there are certain patients with sprue who defy all therapeutic efforts. It is for these chronically and seriously ill patients that we have constantly searched for a new and better form of therapy. With the advent of ACTH and cortisone it has become apparent that a new and effective agent has become available for the treatment of this disease. To the best of my knowledge, the first patient with intractable sprue to receive ACTH therapy was Dr. Almy's[9] patient at the New York Hospital, who was treated in June, 1950, with ACTH. The results were excellent, and I understand that she is now in good health on a maintenance dose of cortisone. Nearly simultaneously, Taylor, Wollaeger

and Comfort[10] at the Mayo Clinic studied the effects of cortisone in sprue and reported balance studies which clearly indicate that cortisone improves intestinal absorption of fat and also depresses fecal loss of nitrogen. Similar results have been reported by other observers, including Colcher, Drachman and Adlersberg.[11] Our own experience with ACTH and cortisone includes observations made on seven patients with sprue. The response of these patients is well exemplified by the thirty-seven year old woman who had the iron-deficiency anemia. She had had intractable sprue since 1944 and had received all the usual forms of therapy but had not responded. When admitted to this hospital in January, 1951, she had all of the classical findings: a flat glucose tolerance curve, steatorrhea of considerable degree, tetany, hypocalcemia, absence of serum carotene, normal vitamin A. She first received a placebo (cholesterol suspension) intramuscularly for one week, without response. Cortisone was then started in a dosage of 200 mg. daily for two days, then 100 mg. daily. On the fifth day she began to improve. The diarrhea diminished, her appetite became much improved and she began to gain weight. Some of this weight gain was water but a true weight gain also occurred. After over a month of treatment with cortisone the dosage was gradually tapered off and she was sent home without cortisone. After twenty days she had a severe clinical relapse with considerable diarrhea and all of the previous manifestations. Cortisone was then resumed and she again very quickly responded and began to gain weight. The diarrhea ceased. We then switched from intramuscular cortisone to oral cortisone, beginning with a placebo that looked like the oral cortisone tablet. After twenty-one days she again relapsed, with severe diarrhea, and felt quite ill. We then had her resume cortisone, 25 mg. twice a day, and there was a very rapid response. The diarrhea ceased. After six months the dose was reduced to 25 mg. It apparently was not enough and she had a clinical relapse in nine days. The dose was increased to 50 mg. and she improved rapidly. On June 2, 1952, cortisone was discontinued. Within sixteen days she had a severe clinical relapse, with weight loss and severe diarrhea. Cortisone by mouth was resumed, with almost immediate response, and she has been maintained on cortisone ever since. We have since been able to reduce the dose to 25 mg. a day by mouth, and she is still on this dosage. At present she is in splendid health and weighs nearly 130 pounds (her weight was 90 pounds when we started). Her serum albumin is now normal. The serum calcium is normal, and this is of interest because she stopped all vitamin D and calcium supplements four months ago. There has been no recurrence of tetany. Her serum carotene has risen to normal, which is a very unusual finding in treated sprue; usually this has been a very persistent and seemingly irreversible defect. The glucose tolerance curve when last checked was within low normal limits.

Her x-ray changes are also of interest, revealing markedly disturbed motor physiology. This was manifested by segmentation or discontinuity of the ingested barium, by a loss of the herringbone pattern which is normal in the upper small bowel, and by flocculation of the barium. These were all very striking. There was also very slow transit of the barium meal; it took seven hours for the barium column to reach the ileocecal valve, the normal transit time being three hours or less. After treatment there was definite improvement, the transit time being reduced to two or two and a half hours, the normal bowel pattern beginning to return. Some abnormality, however, persisted.

Figure 1 is from another sprue patient receiving maintenance doses of cortisone. Before treatment this patient exhibited a bizarre abnormality in small bowel pattern and now has what we would regard as a perfectly normal pattern, with distinct valvulae conniventes and normal motor function.

I do not mean to imply that cortisone therapy should be recommended for all patients with sprue. I believe it should be reserved for those who have failed to respond to the usual measures. The reason for my conservatism is that the very first patient in our series, who received a six-week course of cortisone, ultimately developed disseminated and lethal tuberculosis. There was some question whether inanition due to her severe sprue and a subsequent hepatitis was responsible for this development but one could not escape the feeling that cortisone therapy may have accelerated the process.

DR. DAVID SCHACHTER: I would like to ask Dr. Plimpton whether he can explain the apparent difference in calcium metabolism in tropical and non-tropical sprue.

DR. PLIMPTON: I am glad you brought that out. It has been stated that patients with tropical sprue do not have a low serum calcium. I am

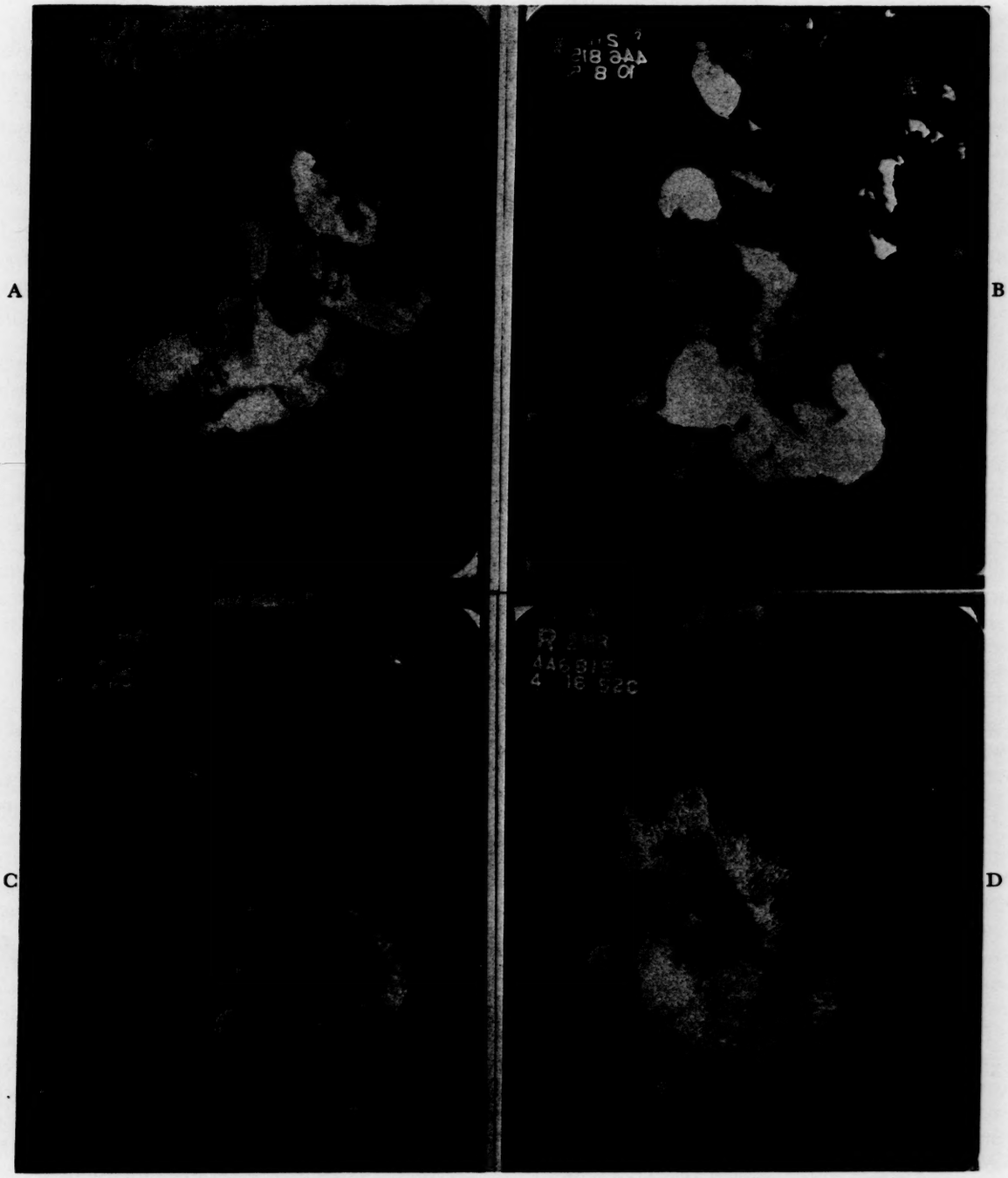


FIG. 1. A forty-six year old woman with severe sprue failing to respond to conventional measures but responding dramatically to cortisone and requiring small maintenance doses of cortisone and, later, smaller doses of hydrocortisone. A and B, October 8, 1951; severe derangement of motor function of the small intestine with a transit time of six hours before cortisone therapy. C and D, April 16, 1952; while on cortisone therapy, a striking return to normal motor function with a normal transit time of two hours.

not at all sure that this is a consistent difference. In the first place, it is hard to know what is meant by tropical sprue. I would assume that it was a steatorrhea occurring in the tropics for which no etiologic parasitic, bacterial or pathologic process can be found. In the second place, there are very few studies which include serum calcium values. Stefanini recently studied about forty Italian prisoners of war in India with tropical sprue and reported serum calcium concentrations ranging from 7 to 9.5 mg. per cent. It would seem entirely reasonable to me that any patient with prolonged steatorrhea might well develop a low serum calcium, and I should think that this reported difference between tropical and non-tropical sprue was one only of degree, possibly related to the duration of the illness.

DR. LEPORE: Dr. Spies, in a recent report, had some figures on calcium levels in tropical sprue and most of them were in the normal range despite severe clinical manifestations of the disease. The general belief is that hypocalcemia is relatively uncommon in tropical sprue.

DR. CROSS: I should like to raise a more fundamental question along these lines, namely, is it conclusively established that there is such an entity as tropical sprue? Certainly, many of the studies of this disease are poorly documented and doubtless include steatorrheas secondary to parasitic infestation, pancreatic steatorrheas and patients such as those Dr. di Sant'Agnese has referred to, who have the constitutional defect he has described with steatorrhea triggered by the tropical environment. It has been my impression that even after eliminating all these cases, some instances of true tropical sprue would remain, but I am not sure of this. Dr. Lepore, do you think there is such an entity as tropical sprue?

DR. LEPORE: Yes, Dr. Cross, I do. I have the impression that extrinsic or environmental factors are much more important in tropical sprue than in the non-tropical form. The response to various medications seems to differ. For example, folic acid usually has a dramatic therapeutic effect in tropical sprue while the response of patients with the non-tropical form is often most disappointing. This suggests that the basic defect may be quite different in many instances in the two forms of the disease.

DR. ROBERT F. LOEB: I would like to ask whether it is not true that, by and large, the original studies of Castle and Rhodes indicated a very satisfactory response to treatment with liver in the endemic sprue areas, a response which one does not see in our group of patients with non-tropical sprue. This would again seem to indicate that they are two distinct diseases—granting that it is very easy for an individual with the constitutional defect underlying non-tropical sprue to develop overt sprue in the tropics.

DR. IRVING LONDON: Yes, that is right, and I think the same thing holds true for what Dr. Lepore just said about folic acid. The response in tropical sprue has always been better than in non-tropical sprue.

DR. HENRY ARANOW: I should like to ask about the present status of the Frazer hypothesis that bacterial invasion of the upper small bowel is a major factor. It was presented here with some eloquence a couple of years ago.

DR. CROSS: I think that theory is now being less enthusiastically championed. There is no doubt that abnormal bacteria flourish in the intestinal tract of sprue patients but the present feeling seems to be that this is a result of the disease rather than its cause. Elimination of the abnormal bacteria by oral administration of antibiotics has no effect on the clinical course of the disease.

DR. LOEB: I wonder if Dr. Lepore or anybody else has any idea of a possible mechanism of action of cortisone in these patients? I think most of us would not feel that people with non-tropical sprue had primary hypoadrenalism.

DR. LEPORE: I am not aware of any theory which satisfactorily explains this effect.

STUDENT: How should pancreatic steatorrhea be treated?

DR. LEPORE: We have been following several pancreatectomized patients and certain basic principles have been evolved in their management. These patients also have a partial gastrectomy since that is part of the operation. In the past, it has been customary to give pancreatic supplementation as enteric-coated tablets. This seemed illogical to us because there was little or no free acid secreted in these patients, and we have therefore used whole pancreatic powder instead. A teaspoonful three times a day with meals is the dose we have generally used. Also, efforts to delay intestinal transit have been worth while in some patients. We have been able to do this with anticholinergic drugs, such as banthine, prantal and

probanthine. They have been helpful agents. We have also used tween 80 in the form of sorlate, 1½ gm. three times daily, and the usual, well recognized dietary measures.

SUMMARY

DR. GILBERT H. MUDGE: In this clinic we have discussed some of the common clinical features as well as certain of the underlying mechanisms in the syndromes associated with malabsorption of ingested food from the intestinal tract. In reviewing the physiology of fat absorption the roles of emulsification, hydrolysis, intestinal lipase activity and routes of absorption have been summarized. Although it has been proposed that the degree of fat hydrolysis determines whether absorption proceeds via the venous or lymphatic routes, there are many factors which complicate direct measurements. Physical absorption as well as active transport may contribute to net absorption. Furthermore, intestinal hydrolysis is not a simple reaction, for resynthesis may occur as an integral part of the cellular mechanism. The route of absorption is also influenced by the molecular weight of the ingested fatty acid. Of related interest is the fact that selective differences in the rate of absorption of sugars are greatly magnified in these disease states.

The causes of steatorrhea are classified on a reasonable physiologic basis. Of major interest are celiac disease and non-tropical sprue, currently regarded as manifestations of the same constitutional defect, with age and other environmental factors playing dominant roles in determining the precise clinical picture. Among the aspects which are here critically reviewed are x-ray studies and other diagnostic procedures, the role of heredity, the realtionship of impaired fat absorption *per se* to the total clinical picture, and the apparent importance of trigger mechanisms, including allergy in some but not all patients. The diagnosis of mild cases is discussed in detail, as is the natural history of underlying mechanisms during symptom-free intervals.

Electrolyte disturbances may sometimes be attributed to exceptional losses of sodium, potassium and water. More frequently defects are seen in the metabolism of calcium, often with tetany and osteomalacia. The theories advanced to explain the abnormalities in calcium absorption are reviewed; no single concept appears satisfactory. There is little agreement on the relative differences in disturbances in calcium metabolism in the tropical and non-tropical forms of sprue.

The treatment of the malabsorption syndrome involves a large number of therapeutic measures, many of them non-specific and others of debatable effectiveness. There appears to be general agreement, however, on the role of proper diet and in the desirability of administering accessory vitamins, especially when overt hematologic abnormalities are present. Newer forms of therapy include the use of detergents to facilitate intestinal absorption and the administration of ACTH or cortisone. Although the mechanism of action of adrenal steroids is not known, they appear to exert a dramatic effect in some cases, and their use appears to be indicated at least in selected patients.

REFERENCES

1. THAYSEN, T. E. H. Non-tropical Sprue. London, 1932. Oxford University Press.
2. LEPORE, M. J. and GOLDEN, R. A syndrome due to deficiency of the vitamin B complex. *J. A. M. A.*, 117: 918, 1941.
3. ANDERSEN, D. H. and DI SANT'AGNESE, P. A. The Celiac Syndrome. In Brenneman, Practice of Pediatrics, vol. 1, chap. 29.
4. ANDERSEN, D. H. and DI SANT'AGNESE, P. A. Idiopathic celiac disease. I. Mode of onset and diagnosis. *Pediatrics*, 11: 207, 1953.
5. DI SANT'AGNESE, P. A. Idiopathic celiac disease. II. Course and prognosis. *Pediatrics*, 11: 224, 1953.
6. DI SANT'AGNESE, P. A. and LEPORE, M. J. Idiopathic celiac disease. III. Relation to idiopathic non-tropical sprue. In preparation.
7. FRAZER, A. C. Fat metabolism and the sprue syndrome. *Brit. M. J.*, 2: 769, 1949.
8. JONES, C. M., CULVER, P. J., DRUMMEY, G. D. and RYAN, A. E. Modification of fat absorption in the digestive tract by the use of an emulsifying agent. *Ann. Int. Med.*, 29: 1, 1948.
9. ALMY, T. P. A refractory case of idiopathic steatorrhea (non-tropical sprue), with observations on the therapeutic effects of salt-poor human albumin and of adrenocorticotropic hormone. *Ann. Int. Med.*, 34: 1041, 1951.
10. TAYLOR, A. B., WOLLAEGER, E. E. and COMFORT, M. W. The effect of cortisone on non-tropical sprue (idiopathic steatorrhea). *Gastroenterology*, 20: 203, 1952.
11. COLCHER, H., DRACHMAN, S. R., and ADLERSBERG, D. Management of intractable sprue with cortisone and adrenocorticotropin (ACTH). *Ann. Int. Med.*, 38: 554, 1953.

End of Medical Center Anniversary Symposium

Reviews

Coma Mechanisms*

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MANY disorders of cerebral function result from metabolic disturbances within the central nervous system. The degree of dysfunction may be correlated with the intensity of the metabolic disturbance and with the importance of the affected portion of brain tissue. If energy deprivation is of sufficient magnitude and duration, regardless of cause, functional disturbances, coma and irreversible cellular damage may result.

TABLE I
CLASSIFICATION OF CEREBRAL METABOLIC DISTURBANCES

I. Substrate Insufficiency
  A. Decreased blood concentration
  B. Reduced cerebral blood flow
  C. Impaired diffusion from capillaries to cells
II. Enzymatic Disturbances
  A. Lack of enzyme activators
  B. Inhibition of enzymatic activity
  C. Dissociation of enzyme oxidation ("uncoupling")
  D. Destruction of enzymes
III. Oxygen Insufficiency
  A. Decreased blood concentration
  B. Reduced cerebral blood flow
  C. Impaired diffusion from capillaries to cells
IV. Multiple Etiologies

In order that cells may perform their various functions and maintain their structural integrity they must be supplied with energy. At body temperature, enzymes are necessary to catalyze the energy yielding reactions between substrate and oxygen. Any disturbance, therefore, which interferes with either substrate supply, enzymatic activity or oxygen supply of cerebral cells must necessarily result in impaired function. Those cerebral cells with the highest metabolic requirements or with the most active turnover of co-factors are first affected by such energy deprivation. Table I presents a classification of cerebral metabolic disturbances based on the mechanisms by which cerebral cells may be deprived of their substrates or may suffer impairment of their enzymatic activity. In the following discussion the pathologic physiology involving these mechanisms will be considered.

GROUP I—SUBSTRATE INSUFFICIENCY

The brain obtains its energy primarily from the oxidation of glucose.[1] It can also oxidize certain amino acids as well as fatty acids which are synthesized within the cerebral cells. Since the energy derived from the oxidation of stored glycogen, amino acids and locally synthesized lipids are insufficient to support cerebral metabolism for any appreciable duration, the brain is highly dependent for its substrate supply on the glucose delivered to it via the circulation. In view of this great dependency of the cerebral cells upon the circulating glucose it is evident that a sufficiently marked reduction in cerebral glucose delivery will result in impairment of cerebral function and, if this impairment is of sufficient magnitude and duration, in coma. Table II presents typical results of cerebral hemodynamics and metabolism observed in patients in whom coma was induced by the administration of insulin, and in whom the comatose state was subsequently terminated by the intravenous administration of glucose.[2] It may be noted that in uncomplicated hypoglycemic coma there is a normal rate of cerebral blood flow and a normal oxygen delivery but a decrease in the rate of cerebral oxygen utilization. That the decrease in cerebral oxygen consumption is due to reduced availability of substrate rather than to a direct enzymatic disturbance is evidenced by its rapid return to normal upon the administration of glucose. Nevertheless, if the hypoglycemia is sufficiently intense and prolonged, irreversible coma may result. Table

* From the Georgetown and George Washington University Medical Divisions, Gallinger Municipal Hospital, Washington, D. C. This investigation was supported by a research grant (PHS H-556C3) from the National Heart Institute of the National Institutes of Health, Public Health Service, and by a research grant from United Cerebral Palsy Foundation.

II presents the data obtained in four subjects in whom the comatose state could not be reversed despite the administration of glucose and subsequent maintenance of high blood sugar levels.[3] In all these cases cerebral oxygen consumption remained depressed until demise despite restoration of an adequate delivery of glucose. The prolonged and intense hypoglycemia resulted in irreparable cellular damage. Presumably, the cortical cells show the greatest damage, as evidenced by the clinical status of such patients who demonstrate cortical depression with released or normal subcortical activity and normal medullary function.[4]

The delivery of glucose to the central nervous system may be impaired by reduction of cerebral blood flow. It is possible that the varying susceptibility to hypoglycemia seen in different individuals is at least partly based on differences in the rate of cerebral blood flow. A subject with a normal cerebral blood flow has delivered to his central nervous system twice as much glucose per unit time as does another subject with the identical blood sugar level but only half the usual rate of blood flow. Perhaps this is the explanation for the fact that some elderly diabetic subjects, with arteriosclerosis resulting in lowered cerebral blood flow, develop hypoglycemic symptoms at normal blood sugar levels. Another possibility is that the concentration of the metabolite in the blood may not reflect the concentration at cellular levels be-

TABLE II

CEREBRAL HEMODYNAMICS AND METABOLISM IN VARIOUS STATES

Classification	Condition	$CMRO_2$	CBF	CDO_2	CD Glucose	Mental State—Remarks
Normal[25]	.....	3.5	54.0	8.0	54.0	Alert
Substrate insufficiency	Hypoglycemia[2]	1.9	63.0	10.5	4.8	Comatose
	After glucose[2]	3.4	56.0	9.0	10.8	.....
	Post-hypoglycemic coma[3]	1.5	52.0	5.4	186.9	Comatose
Enzymatic disturbances	Diabetic coma[13]	1.7	65.0	11.7	358.8	Comatose
	Hepatic coma *	2.1	43.0	4.2	.....	Comatose
	Uremic coma[16]	2.1	45.0	5.9†	.....	Comatose; hypertensive vascular disease
		2.2	57.0	7.1†	.....	Comatose; no hypertensive vascular disease
	Barbiturate coma *	2.3	51.0	7.0	.....	Comatose
	Alcoholism *	2.7	68.0	7.0	.....	Intoxication; ethanol level 138 mg. %
	Delirium tremens[23]	2.4	34.0	6.3†	.....	Confused
	Wernicke's encephalopathy *					
	Before vitamin therapy	2.2	41.2	4.9	.....	Confused
	After vitamin therapy	2.7	43.2	5.7	.....	
	Pernicious anemia[8]					"Good correlation between
	Before therapy	2.2	91.0	...	.....	changes in mental status and
	After therapy	2.8	40.0	...	.....	$CMRO_2$"
Oxygen insufficiency	Strangulation *	1.7	36.0	5.5	49.7	Comatose
	Cardiac arrest *	1.8	28.0	4.4	.....	Comatose
	Cerebral arteriosclerosis[25]	2.1	34.0	5.2	.....	Confused
	Cerebral arteriosclerosis[26]	2.8	42.0	7.1	.....	Confused
Multiple etiologies	Brain tumors[27]	2.5	34.0	6.2	.....	Comatose
	Traumatic coma, irrev. *	1.8	30.0	4.0	.....	Comatose

$CMRO_2$ signifies cerebral oxygen consumption in cc./min./100 gm. of brain; CBF, cerebral blood flow in cc./min./100 gm. of brain; CDO_2, cerebral oxygen delivery in cc./min./100 gm. of brain; CD Gluc., cerebral delivery of glucose in mg./min./100 gm. of brain.

* Unpublished data of authors.

† CDO_2 estimated from data.

cause of some impairment in the diffusion of glucose from blood to the cells.

GROUP II—ENZYMATIC DISTURBANCES

There is still considerable discussion regarding the pathways through which glucose is oxidized by the cerebral cells. The assumed reactions may be grouped as shown in Figure 1. The first stage involves the anaerobic degradation of glucose to pyruvic acid (Embden-Meyerhoff cycle); the second, the condensation of active acetyl with oxalacetate to form citrate, which undergoes a series of reactions (tricarboxylic acid cycle of Krebs) involving dehydrogenation, decarboxylation and the addition of water or phosphate. The hydrogen yielded as a result of these reactions is received by various hydrogen acceptors and finally combines with oxygen to form H_2O. As a result of these reactions, energy is liberated in the form of high-energy phosphate compounds.

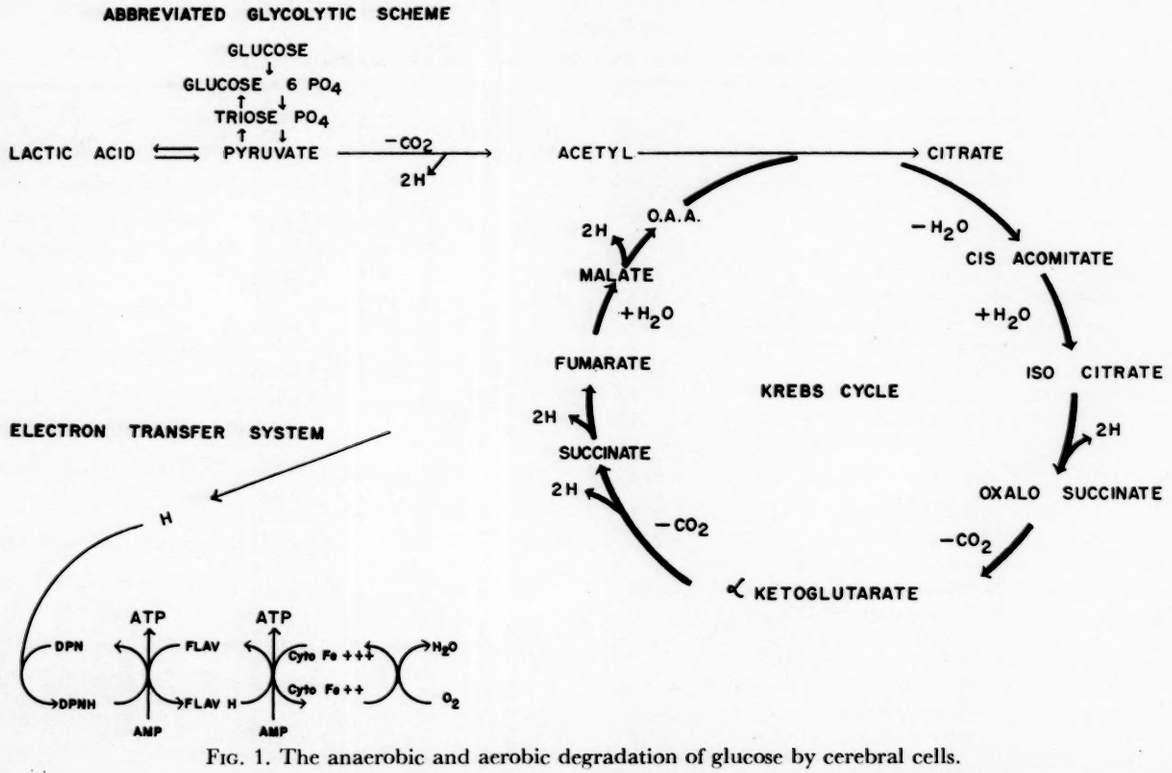

FIG. 1. The anaerobic and aerobic degradation of glucose by cerebral cells.

Various enzymes and co-enzymes are required to catalyze these reactions. Interference with their activity either by specific inhibitors or a lack of necessary activators will impair glucose utilization and result in decreased energy formation and altered activity of the central nervous system. In Table III are listed some of the enzymes concerned with the oxidation of glucose along with their known inhibitors or activators.

Disturbances of consciousness following the administration of specific inhibitors is relatively sudden while that resulting from a lack of an essential activator (vitamin deficiency) is usually insidious in its development, and coma may occur only with advanced deficiency states. If an acute and complete deficiency of activators could be produced by competition or blocking, one might anticipate a sudden onset of coma. Examples of some of the more common cerebral metabolic disorders resulting from disturbed enzyme activity are considered.

LACK OF ENZYME ACTIVATORS

Many of the glycolytic and respiratory enzymes consist primarily of two components—a protein moiety which is substrate specific and the co-enzyme, a non-protein portion which is reaction specific. Some of the vitamins, particularly the "B" vitamins, function as co-enzymes in the enzymatic degradation of carbohydrate. As previously indicated, interference with the activity of selected areas of the central nervous

system rather than coma is most commonly observed in the various deficiency states. This is most likely due to the greater requirement of these areas for the vitamin or because there is greater destruction of the co-factors by specific enzymes. The patient usually succumbs because of the manifestation of the deficiency state elsewhere in the body or from complications resulting from the poor nutritional state. Irreversible cellular damage does not usually result from enzymatic disturbances, probably because cellular requirements for energy are considerably reduced.

Thiamin Deficiency. Thiamin functions as the co-enzyme for the decarboxylation of α-keto-acids (pyruvic and α-ketoglutaric acid.)[5] The ingested thiamin is esterified with phosphate to cocarboxylase. Cocarboxylase, lipoic acid and magnesium, together with a specific protein, constitute the enzyme for the oxidation of keto acids.

The central nervous system disturbances associated with a deficiency of vitamin B_1 are referred to as Wernicke's syndrome. This syndrome is probably a combination of several nutritional deficiencies, but the predominant factor is a severe and acute form of thiamin deficiency. *In vitro* studies using brain slices from pigeons with avitaminosis B_1 have revealed an accumulation of pyruvic acid, decreased cerebral oxygen consumption and a lowered respiratory quotient.[6] Upon the addition of thiamin to the fluid medium there results a disappearance of pyruvic acid and a return to normal of the oxygen consumption and respiratory quotient. In Table II are presented the cerebral hemodynamics and metabolism of a typical case of Wernicke's syndrome before and after treatment with vitamin B_1. It may be seen that the cerebral metabolic rate returns toward normal following the administration of vitamin B_1.

Niacin Deficiency. The amide of nicotinic acid is an integral part of diphosphopyridine nucleotide (DPN, co-enzyme 1) and triphosphopyridine nucleotide (TPN, co-enzyme 2). The pyridine nucleotides act as water-soluble acceptors and transporters of the hydrogen liberated by dehydrogenation reactions. (Fig. 1.) The reactions in which these co-enzymes participate are indicated in Table III.

The mental changes associated with chronic niacin deficiency (pellagra) have long been recognized. According to Jolliffe,[7] the syndrome of acute niacin deficiency is characterized by unconsciousness, sucking, grasp reflexes and cogwheel rigidity. Unfortunately, quantitative studies of cerebral metabolism of subjects with acute or chronic niacin deficiency have not been made but one would anticipate a reduced cerebral metabolic rate and a normal cerebral glucose and oxygen delivery.

TABLE III
CEREBRAL ENZYMES, INHIBITORS AND ACTIVATORS

Enzymes	Inhibitors	Enzyme Activators or Co-factors
Hexokinase	Pituitary and adrenal cortical extracts	Insulin (?)
Triosephosphate dehydrogenase	Iodo-acetic acid	Diphosphopyridine nucleotide and glutathione
Pyruvic oxidase	Arsenite (other heavy metals)	Thiamin, nicotinamide, lipoic acid, pantothenic acid
Isocitric dehydrogenase	Iodo-acetic acid (?)	Triphosphopyridine nucleotide
α-ketoglutaric dehydrogenase	Arsenite (other heavy metals)	Thiamin, nicotinamide, lipoic acid, pantothenic acid
Malic dehydrogenase	.....	Diphosphopyridine nucleotide
Cytochrome C reductase	Barbiturates (?) Atabrine	Flavin adenine dinucleotide
Cytochrome oxidase	Cyanide and carbon monoxide	.....
Phosphorylase	.....	Adenylic acid
Enolase	Fluoride	Magnesium
Lactic dehydrogenase	.....	Diphosphopyridine nucleotide
Succinodehydrogenase	Malonic acid	.....

Pantothenic Acid Deficiency. This B-vitamin is part of "co-enzyme A" which is essential for the condensation of oxalacetate (dicarboxylic acid) and acetate to form citrate (tricarboxylic acid), the starting point of aerobic oxidation(Krebs cycle). The acetyl co-A-enzyme complex is also concerned with acetylation of aromatic amines and possibly with the synthesis of such compounds as cholesterol, fatty acids and steroid hormones.[5] In view of the key position of this co-enzyme in oxidation of glucose and its importance in biosynthesis, one wonders why cerebral disturbances resulting from pantothenic acid deficiency are not observed. Cases of isolated pantothenic acid deficiency in humans have not been reported, and in animals neurologic manifestations have been reported only in suckling pigs. It may be that the turnover rate of Co-A is too slow to develop deficiency symptoms in adult animals.

Vitamin B_{12} Deficiency. The observation that central nervous system disturbances may be

manifest in pernicious anemia with little or no evidence of hematologic involvement (anemia) strongly suggests that vitamin B_{12} may in some way be necessary for normal cerebral cellular activity. Scheinberg[8] has shown that in subjects with pernicious anemia with minimal blood changes there was a decreased oxygen and glucose utilization. A good correlation between the mental status defects, the severity of the neurologic involvement and the cerebral oxygen consumption was also noted. The administration of vitamin B_{12} or liver extract resulted in a moderate increase in cerebral oxygen consumption and in varying degrees of clinical neurologic improvement but in no instance did it return to normal, suggesting that a part of the cellular damage may have been permanent. The role of vitamin B_{12} has not yet been determined but it may function as a co-enzyme for a specific oxidative reaction or for the synthesis of an essential intermediate.

Inhibition of Enzymatic Activity

Heavy Metal Poisoning. "Toxic encephalitis" may result from the administration of heavy metals, particularly lead and arsenic. The mechanisms by which heavy metals alter the function of the central nervous system is not well understood, although it has long been apparent that there are many similarities between the signs and symptoms of heavy metal poisoning and vitamin B_1 deficiency. It is now recognized that heavy metal compounds, and perhaps other "general protoplasmic poisons," may act by combining with the thiol groups of tissue enzymes or co-enzymes.[9] Recently a "pyruvic acid oxidase" factor which catalyzes oxidation of pyruvic acid and α-ketoglutaric acid has been demonstrated.[10] This factor (lipoic acid) contains two sulfhydryl radicals which, when combined with a heavy metal such as arsenic, form a stable ring compound in which the activity of the sulfhydryl group is lost. The importance of sulfhydryl compounds in intermediate carbohydrate oxidation renders the brain particularly vulnerable to heavy metal poisoning. Peters and co-workers,[9] using cerebral tissue *in vitro*, have demonstrated a reduction of cerebral oxygen consumption by heavy metals (arsenic) which is reversed by the addition of thiol compounds to the fluid medium. The dramatic results obtained in early cases of arsenical encephalopathy by the use of dithiopropanol (BAL)[11] lends clinical support to the fundamental observations of Peters. Studies of cerebral hemodynamics and metabolism of patients with encephalopathy due to heavy metals have not been reported.

Diabetic Coma. Cori and co-workers[12] have shown that insulin overcomes the inhibitory action of anterior pituitary and adrenal cortical secretions on the enzyme hexokinase (obtained from yeast and muscle) and in this way favors the formation of glucose-6-phosphate. Insulin may also catalyze the reactions of other carbohydrate intermediates as well as the synthesis of fat from carbohydrate. However, it is questionable whether insulin is necessary for the oxidation of glucose by cerebral cells since brain hexokinase is not inhibited by either anterior pituitary or adrenal cortical extracts. Nevertheless, in diabetic coma[13] the cerebral oxygen consumption is markedly depressed. (Table II.) Since the cerebral blood flow, vascular resistance and oxygen delivery may be normal, and glucose delivery is usually far greater than normal, this depression of the cerebral metabolic rate must be attributed to inhibition of cerebral enzymatic activity. The mechanism of this inhibition is not known; there is no support for the contention that diabetic coma is due to the accumulation of ketone bodies or to disturbances in water and electrolyte metabolism. Recently Weil-Malherbe[14] has demonstrated a substance present in the plasma of patients in diabetic coma that inhibits hexokinase activity.

Uremic and Hepatic Coma. In both these conditions there is an accumulation of "noxious substances" as a result of impaired excretory and detoxification mechanisms, as well as marked disturbances in water and electrolyte metabolism. The observation that uremic coma in some instances may be reversed by dialysis with the artificial kidney suggests that coma may be due to hematogenous inhibition of cerebral enzymatic activity. We are not aware of dialysis studies on patients with hepatic coma. Davidson et al.[15] noted clinical and electroencephalographic changes similar to those observed in hepatic coma following the administration of ammonium cation exchange resin to cirrhotic subjects. They suggest that these patients are unable to remove the circulating ammonium ion and consequently suffer from ammonia intoxication. It should be pointed out that not all patients in hepatic coma have significant elevation of their blood ammonia. Nevertheless, it appears that in uremic and hepatic coma there

is a breakdown of carbohydrate metabolism due to inhibition of enzymatic activity. Studies of cerebral hemodynamics and metabolism of patients in uremic[16] and hepatic coma tend to confirm this impression and have disclosed adequate vascular delivery of glucose and oxygen but a depressed cerebral metabolic rate. (Table II.) The etiologic factor or factors as well as the specific enzymes inhibited are as yet unknown.

Enzyme Inhibition and/or Uncoupling

Barbiturates and Alcohol. There is considerable speculation regarding the mechanism for coma following the ingestion of narcotics. The bulk of our present knowledge pertaining to the interaction of barbiturates and enzymes stems from the work of Quastel and co-workers[17] who showed that the barbiturates may reversibly inhibit the oxidation of glucose, lactate and pyruvate by cerebral tissue. Inhibition of oxidation by cerebral tissue has also been demonstrated following the addition of alcohol[18] to respiring brain tissue suspensions. The exact site in the oxidative system at which these narcotics act is not known. There is evidence that cytochrome C reductase is sensitive to barbiturates while some believe that the pyruvic oxidase system is most sensitive and that it is the dehydrogenase moiety which is inhibited.

Studies *in vivo* have to a certain extent confirmed the observation of a depression of the cerebral metabolic rate following the ingestion of barbiturates and alcohol. In patients who ingested large doses of barbiturates for suicidal purposes we have noted a significant depression of the cerebral metabolic rate and its return to normal as the clinical condition of the patient improved. (Table II.) Patterson and co-workers have noted similar findings in patients hospitalized for delirium tremens.[19] It is difficult to ascertain whether in the latter studies the depression is due to the alcohol ingested, a concomitant avitaminosis, cerebral edema or to a combination of these factors.

The question has been raised as to whether a depression of cerebral oxidation is the only mechanism by which these substances may inhibit cerebral activity. Himwich and co-workers[20] have shown that the cerebral metabolic rate is not measurably depressed by the administration of barbiturates until deeper levels of anesthesia are reached and then considerable functional depression can be observed before a depression of the cerebral metabolic rate is demonstrated. Similarly, the intravenous administration of alcohol in concentrations sufficient to raise the blood level to approximately 150 mg. per cent does not significantly influence cerebral hemodynamics and metabolism, yet causes marked alterations in the functional activity of the central nervous system (Table II) as manifested by signs of intoxication.

There may be several explanations for these observations. It is possible that the available technics are not sufficiently sensitive to detect the small changes in oxidation that may be adequate to cause marked changes in "functional" activity. These narcotics, on the other hand, may selectively inhibit particular areas of the central nervous system and this inhibition, though marked locally, is not reflected in total cerebral metabolism studies. Bain[21] has suggested that in those cases in which no inhibition of oxidation is evident the functional impairment of the central nervous system may be due to "uncoupling," i. e., a dissociation of the process of the formation of high energy phosphate bonds from oxidation, when oxidation may proceed at a normal or perhaps a slightly accelerated rate but adenosinetriphosphate (ATP) formation may be completely inhibited. This phenomenon applies almost exclusively to coenzyme oxidation whereas substrate level phosphorylation is unaffected. Barbiturates, alcohol and perhaps other substances may induce "uncoupling" by interacting with transfering enzymes which mediate the synthesis or breakdown of adenosinetriphosphate. That there may be a loss of functional activity in the presence of normal oxidation has been demonstrated by the work of Taggart[22] who showed that the renal tubular excretion of para-amino hippurate, diodrast and phenol red was markedly reduced following the administration of dinitrophenol. No significant changes in renal hemodynamics were observed. Since dinitrophenol exerts no depressant effect on respiration at the concentrations employed, its inhibitory effect on transport mechanisms is attributed to an interruption of aerobic phosphorylation reactions.

Destruction of Enzymes

Comas associated with virus infection, and possibly the degenerative diseases of the central nervous system, may be due primarily to a destruction or inactivation of enzymes essential for neuronal activity. The studies of Racker and co-workers[23] showed that mice infected with

the Lansing strain of poliomyelitis virus and those infected with the Theiler FA strain of mouse encephalitis virus showed an impairment of brain glycolysis. The glycolytic enzyme found to be affected was triosephosphate dehydrogenase; its addition in crystalline form restored the glycolytic activity of the infected brain homogenates to normal. Addition of a ferrous ion to normal brain homogenates caused a similar inhibition of the triosephosphate dehydrogenase. It is believed that a ferrous ion, liberated as a result of the infection, activates a proteolytic enzyme present in normal brain which in turn inactivates triosephosphate dehydrogenase.

GROUP III—OXYGEN INSUFFICIENCY

The adult brain cannot function for even short periods of time anaerobically but must be constantly supplied with oxygen to meet its metabolic requirements. The oxygen utilization by the adult brain is approximately 50 cc./100 gm./min. It has been estimated that at any moment the brain and the blood circulating through it contain about 7 cc. of oxygen, an amount sufficient to supply the needs of the brain for less than ten seconds. It can be anticipated, therefore, that oxygen deprivation from whatever cause, for even short periods of time, will result in functional and structural changes in the central nervous system. This fact is dramatically illustrated by the experiments of Rossen, Kabat and Anderson[24] in which the human brain was temporarily deprived of oxygen by sudden and complete arrest of the cerebral circulation. Consciousness was lost in six to seven seconds; restoration of the cerebral circulation within 100 seconds was followed by a rapid return of consciousness and no objective evidence of brain injury. However, there are many documented cases in which irreversible coma ensued as a result of strangulation or sudden cardiac arrest for only a matter of minutes. Except for the time factor (due to the larger stores of carbohydrate than oxygen), the effects of oxygen deprivation and hypoglycemia on the central nervous system are clinically and pathologically similar. This is not surprising since both substances are essential for normal carbohydrate oxidation by the central nervous system, participating at the beginning and end of the oxidative chain. As can be seen in Figure 1, oxygen functions as an acceptor of hydrogen transferred to it by the electron system.

The delivery of oxygen to the central nervous system depends on: (1) the concentration of oxygen in the arterial blood, (2) the rate of cerebral blood flow, (3) the facility of oxyhemoglobin dissociation and (4) a factor "X" representing the permeability of the blood-brain-barrier. A disturbance of any of the above mechanisms could conceivably lead to a loss of consciousness and, if sufficiently severe or prolonged, to irreversible damage of cerebral cells. There are certain compensatory mechanisms operating to correct, at least in part, any deficiency in the oxygen supply to the brain. During periods of hypoxia there may be reflex elevation of the blood pressure peripherally, changes in cardiac output and reflex shunting of blood from the less important organs to the brain. Locally there are reflex and chemical influences that tend to regulate the rate of cerebral blood flow by changing the caliber of the cerebral vessels. The extent to which oxygen delivery must fall before cerebral metabolism is impaired is not known and undoubtedly varies with the age and the clinical state of the patient.* It is generally agreed that the higher brain areas, i.e., those with the greatest metabolic rate, are most sensitive to oxygen lack. It has been estimated that the cerebral cortex becomes irreversibly damaged after five to ten minutes of complete anoxia; whereas the medulla may function effectively after total anoxia of from twenty to thirty minutes' duration. The above observations are borne out clinically in cases of cardiac arrest, following which cortical dysfunction, subcortical release and normal medullary function have been observed. Cerebral hemodynamics and metabolism of several cases with irreversible posthypoxic coma are presented which illustrate mechanisms whereby the delivery of oxygen to the cerebral cells may be impaired.

Decreased Blood Concentration. Acute reduction of the arterial oxygen content by either a decrease of environmental oxygen or an interference with the passage of oxygen to the alveolar capillaries will, if sufficiently intense, reduce the delivery of oxygen to the central nervous system. The cerebral hemodynamics and metabolism of a subject who developed irreversible cerebral

* In recent observations in which hypotension was acutely induced by the administration of hexamethonium, we noted that when the cerebral blood flow fell to between 30 to 40 cc./100 gm. of brain/minute, signs and symptoms of cerebral ischemia became manifest.

damage and coma as a result of strangulation, estimated to have persisted for ten minutes, are shown in Table II. The patient survived for five days never regaining consciousness and exhibited many features resembling decortication. Studies of cerebral hemodynamics on the third and fourth day disclosed a normal cerebral blood flow and normal cerebral vascular resistance but a decreased cerebral metabolic rate. Although strangulation may impair to some extent the cerebral blood flow by compressing the carotid vessels and also interfere with the elimination of CO_2 by tracheal compression, we believe that the major factor responsible for the irreversible coma in this case was the prolonged reduction in partial pressure of oxygen.

Reduced Cerebral Blood Flow. The delivery of oxygen to the central nervous system may also be reduced by any mechanism which curtails the flow of blood through the cerebral vessels. Stagnant cerebral hypoxia is undoubtedly responsible for syncope or coma as seen in acute reduction of cardiac output (aortic stenosis, coronary occlusion, Stokes-Adams syndrome, secondary shock, etc.). The effects on cerebral hemodynamics and metabolism of a destructively prolonged episode of stagnant cerebral hypoxia due to decreased oxygen delivery to the brain are seen in a patient who had cardiac arrest for approximately eight minutes. (Table II.) The studies were performed on several occasions approximately one month following the incident. Despite the subsequent normal oxygen delivery the cerebral metabolic rate has remained depressed.

Local cerebral stagnant hypoxia, observed in cerebral vascular disease (arteriosclerosis, cerebral thrombosis and cerebral embolism), is frequently associated with a loss of consciousness. In such cases coma is most likely the result of ischemia of selected areas of the brain (thalamus). In elderly alert patients with cerebral arteriosclerosis[25] and thrombosis the values observed for cerebral blood flow and metabolism are not significantly different from those noted for comatose patients with similar diagnoses.

GROUP IV—COMA OF MULTIPLE ETIOLOGIES

We have shown how substrate deprivation, enzymatic disturbances and impaired oxygen delivery may independently cause coma. It should be mentioned that in some conditions more than one of those etiologic factors may be operating simultaneously, yet their effects may be additive.

For example, in coma due to a space-occupying lesion of the central nervous system the delivery of oxygen and glucose may be impaired by obstruction of vascular channels as a result of their invasion and distortion by herniation of portions of the brain, by thrombosis of veins, by reactive spasm of arteries or by increased intracranial pressure. Diffusion of essential substrates may be impaired because of altered tensions in the extra- and intracellular spaces and their utilization may not be possible because of disrupted cellular surfaces or actual cellular destruction. The lowered cerebral blood flow and metabolic rate noted in unconscious patients with brain tumors may result from a combination of the above factors.[27]

Perhaps in irreversible coma due to traumatic head injuries many of the same factors may be operating as in coma due to space-occupying lesions. We have had the opportunity to study cerebral hemodynamics and metabolism in six such cases of coma following overt trauma to the head. (Table II.) In all cases studied except one there was a reduction in cerebral blood flow and an increase in cerebral vascular resistance. All patients showed a marked reduction of the cerebral metabolic rate. It cannot be stated whether the decreased cerebral metabolic rate in these cases is due to the reduced cerebral blood flow or if it represents a cellular disturbance resulting from the trauma, or both. There is evidence that in those states associated with considerable destruction of cerebral tissue the low cerebral blood flow may result from the loss of intrinsic homeostatic mechanisms normally initiated by actively respiring tissue.

In many of the conditions discussed the clinical state of coma may be due primarily to localized disturbances. Neurologists have long been aware that there exists a critical area in the region of the third ventricle or mid-brain in which small lesions produce unconsciousness. In the sudden momentary loss of consciousness seen in petit mal seizures, all normal brain rhythms become extinguished suddenly over both hemispheres and are replaced by the familiar wave and spike discharge. One should not assume that these impaired states of consciousness necessarily represent some impairment in metabolic function of the brain as a whole since it is possible to produce similar changes by specific and restricted lesions in the brain

stem in regions which do not necessarily affect the metabolism of the brain as a whole.

SUMMARY

A physiologic classification of cerebral metabolic disturbances is presented, based on the premise that energy required for functional activity and structural integrity of cerebral cells results from enzymatically catalyzed reactions between glucose and oxygen. Insufficiency of glucose (preferential substrate of the cerebral cells) or oxygen, or inhibition or lack of essential enzymes necessary for the degradation of glucose will result in cerebral metabolic disturbances. The variable response of the central nervous system to the deprivation of these essential substances is believed to be due to their availability and differential rates of utilization by various areas of the central nervous system. Clinical examples along with observations of cerebral hemodynamics and metabolism of representative disturbances for each group are presented wherever possible.

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REFERENCES

1. Himwich, H. E. and Nahum, L. H. Respiratory quotient of the brain. *Am. J. Physiol.*, 101: 446–453, 1932.
2. Kety, S. S., Lukens, F. D. W., Woodford, R. B., Harmel, M. H., Freyhan, F. A. and Schmidt, C. F. The effects of insulin hypoglycemia and coma on human cerebral metabolism and blood flow. *Federation Proc.*, 7: 64, 1948.
3. Fazekas, J. F., Alman, R. W. and Parrish, A. E. Irreversible post-hypoglycemic coma. *Am. J. M. Sc.*, 222: 640–643, 1951.
4. Himwich, H. E., Frostig, J. P., Fazekas, J. F. and Hadidian, Z. Mechanism of symptoms of insulin hypoglycemia. *Am. J. Psychiat.*, 96: 371–385, 1939.
5. Lipman, F. Biosynthetic mechanisms. The Harvey Lectures. Series xliv, 1948–49, Springfield, Ill., 1950. Charles C Thomas.
6. Peters, R. A. Biochemical lesion in vitamin B_1 deficiency; application of modern biochemical analysis in its diagnosis. *Lancet*, 1: 1161–1165, 1936.
7. Joliffe, N., Bowman, K. M., Rosenblum, L. A. and Fein, H. D. Nicotinic acid deficiency encephalopathy. *J. A. M. A.*, 114: 307, 1940.
8. Scheinberg, P. Cerebral blood flow and metabolism in pernicious anemia. *Blood*, 6: 213–227, 1951.
9. Peters, R. A., Stocken, L. A. and Thompson, R. H. S. British anti-lewisite (BAL). *Nature, London*, 156: 616–619, 1945.
10. Reed, L. J., Debusk, B. G., Gunsalus, I. C. and Schnakenberg, G. H. F. Chemical nature of alpha-lipoic acid. *J. Am. Chem. Soc.*, 73: 5920, 1951.
11. Eagle, H. and Magnuson, H. J. Systemic treatment of 227 cases of arsenic poisoning (encephalitis, dermatitis, blood dyscrasias, jaundice, fever) with 2,3-dimercaptopropanol (BAL). *Am. J. Syph., Gonor. & Ven. Dis.*, 30: 420–441, 1946.
12. Cori, C. F., Price, W. H. and Colowick, S. P. Effect of anterior pituitary extract and of insulin on hexokinase reaction. *J. Biol. Chem.*, 160: 633–634, 1945.
13. Kety, S. S., Polis, B. D., Nadler, C. S. and Schmidt, C. F. The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. *J. Clin. Investigation*, 27: 476–514, 1948.
14. Weil-Malherbe, H. Inhibitor of hexokinase in plasma of diabetics. *Nature, London*, 165: 155, 1950.
15. Philips, G. B., Schwartz, R., Gabuzda, G. J., Jr. and Davidson, C. S. The syndrome of impending hepatic coma in patients with cirrhosis of the liver given certain nitrogenous substances. *New England J. Med.*, 247: 239–246, 1952.
16. Heyman, A., Patterson, J. L., Jr. and Jones, R.W., Jr. Cerebral circulation and metabolism in uremia. *Circulation*, 3: 558–563, 1951.
17. Quastel, J. H. Respiration in the central nervous system. *Physiol. Rev.*, 19: 135–183, 1939.
18. Himwich, H. E., Sykowski, P. and Fazekas, J. F. The effects of alcohol and pentobarbital on metabolism of excised cerebral tissues of adult and infant rats. *Am. J. Physiol.*, 129: 382–383, 1940.
19. Battey, L. L., Patterson, J. L. and Heyman, A. Effects of methyl and ethyl alcohol on cerebral blood flow and oxygen consumption. Presented at Southern Sectional Meeting of American Federation for Clinical Research in Atlanta, Georgia, January 18, 1952; abstracted. *Am. J. Med.*, 13: 105, 1952.
20. Himwich, H. E. Brain Metabolism and Cerebral Disorders. Baltimore, 1951. Williams and Wilkins.
21. Bain, J. A. Enzymatic aspects of barbiturate action. *Federation Proc.*, 2: 653–658, 1952.
22. Taggart, J. V. and Forster, R. P. Renal tubular transport: effect of 2,4-dinitrophenol and related compounds on phenol red transport in the isolated tubules of the flounder. *Am. J. Physiol.*, 161: 167–172, 1950.
23. Racker, E. Metabolism of cell-free brain preparations, p. 70. In The Biology of Mental Health and Disease. New York, 1952. Paul B. Hoeber, Inc.
24. Rossen, R., Kabat, H. and Anderson, J. P. Acute arrest of cerebral circulation in man. *Arch. Neurol. & Psychiat.*, 50: 510–529, 1943.
25. Fazekas, J. F., Alman, R. W. and Bessman, A. N. Cerebral physiology of the aged. *Am. J. M. Sc.*, 223: 245–257, 1952.
26. Freyhan, F. A., Woodford, R. B. and Kety, S. S. Cerebral blood flow and metabolism in psychoses of senility. *J. Nerv. & Ment. Dis.*, 113: 449–456, 1951.
27. Kety, S. S., Shenkin, H. A. and Schmidt, C. F. Effects of increased intracranial pressure on cerebral circulatory functions in man. *J. Clin. Investigation*, 27: 493–499, 1948.

The Toxic Psychoses and Allied States*

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THE toxic psychoses are problems in diagnosis and management common to all the medical specialties. It is the physician without specialty training in psychiatry who usually sees patients who have become delirious in the course of a disease or the treatment thereof. A toxic psychosis is a dramatic, unexpected and almost unpredictable complication, requiring prompt and skillful countermeasures. This paper will attempt to offer guidance in the recognition, evaluation and management of these emergencies.

The term "toxic psychosis" is used here to include all important breaks with reality due to noxious products or to the absence of an essential metabolite. The psychosis is manifested by a delirium with variable clouding of the consciousness. Not infrequently a catatonic stupor, manic excitement, paranoid agitation or a vivid hallucinosis will dominate the clinical picture. There may be some who object to the word "psychosis" to describe a temporary confusional state in an otherwise stable individual. Since disruption of psychologic homeostasis can be achieved with a drug as well as with emotional stress, it seems consistent to think of any major toxic mental aberration as a psychosis.

It is a useful concept to consider that each of us has a psychotic threshold beyond which there is a break with reality. This threshold can be exceeded by a variety of stresses. It varies widely with the individual and with his changing emotional and situational adjustments. The capacity of a given toxin to produce a psychosis in a test group could therefore be represented by a normal bell curve, with a small number extremely susceptible, a similar number very resistant and the bulk of the group distributed in the intermediate position.

ETIOLOGY

When the individual agents are discussed, we shall see that the final common cause of the toxic psychoses is some distortion of cerebral cellular metabolism. Hypoxia of the brain's higher centers is a frequent mechanism. The cortex is also sensitive to disturbances of carbohydrate metabolism. These may consist of inhibition of enzymatic processes, depletion of intercellular glucose, or retention of end products. Excessive deviations of water, electrolyte or protein balance adversely affect the brain cell. There is, in addition, a group of substances which appears to exert a specific histotoxic action on nerve cell protoplasm.

The pathologic counterpart of this metabolic dysfunction is cerebral edema. This often is the only change noted at necropsy in patients expiring during a toxic psychosis. Cytoplasmic and nuclear condensations are less frequent.

A tentative etiologic classification of the more common toxic psychoses is attempted as follows:

The Toxic Psychoses. Exogenous factors: (1) Those producing cerebral anoxia: carbon monoxide; thiocyanate; lowered atmospheric oxygen tension as in mountain sickness; antabuse. (2) Those interfering with carbohydrate metabolism or the respiratory enzyme systems: sedatives such as chloral, barbiturates, bromides; anesthetics as ether, chloroform, alcohol, nitrous oxide; narcotics such as morphine, meperidine, marihuana; insulin; thiamine deficiency; nicotinic acid deficiency. (3) Those producing cerebral electrolyte and water disturbances: ACTH and cortisone; heat exhaustion and low salt syndrome; thirst and dehydration; starvation. (4) Those having selective effects on the brain cell, or whose mode of action is in doubt: digitalis and its glucosides; atabrine; benzedrine and related substances; atropine and related substances; mescaline and lysergic acid derivatives; sulfonamides; antibiotics.

Endogenous factors: (1) Those producing cerebral anoxia: the primary anemias; anemias of blood loss; advanced diffuse pulmonary disease; congestive heart failure; shock. (2) Those producing interference with carbohydrate, water

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and electrolyte metabolism: Addison's disease; Cushing's syndrome; hypoparathyroidism; hyperparathyroidism and vitamin D intoxication; myxedema; thyrotoxicosis; diabetic acidosis; hyperinsulinism. (3) Those due to accumulation of abnormal metabolites, or to exhaustion states: infections such as pneumonia, typhoid, malaria, influenza, rheumatic fever and typhus; uremia; cholemia; the postoperative and puerpural states; eclampsia; porphyria.[1]

Of these agents, those of the greatest clinical significance will be considered in detail.

EXOGENOUS SUBSTANCES CAPABLE OF PRODUCING A PSYCHOSIS

Antabuse. An example of the multiplicity of agents influencing the transition into a psychosis is seen during antabuse therapy.[2–6] These patients are an emotionally disturbed group who have developed abnormal responses to frustration, guilt and inadequacy. Some of them are latent schizophrenics. When the crutch of alcohol is removed, a psychotic breakdown is quite possible. Furthermore, there is evidence that tetraethylthiuram alone, or combined with alcohol, can mobilize a toxic psychosis. No characteristic pattern is discernible but premonitory symptoms include drowsiness, memory defects and depression. After the psychosis has appeared, stopping the drug will produce recovery and resumption of the drug in smaller doses may be tolerated. It would be well to bear in mind that previous alcoholic or traumatic brain damage may be present.

Barbiturates. The barbituric acid derivatives are a frequent cause of toxic deliria. There are individuals hypersensitive to these drugs who repeatedly become inebriated on ordinary doses. Patients given barbiturates for severe pain may become unmanageable. Liver damage will retard the detoxification of the short-acting barbiturates, resulting in recirculation of these products which can narcotize the patient for longer periods than the physician anticipated.

As a rule, acute barbiturate poisoning is followed by coma rather than delirium. Chronic barbiturism is similar in its neuropsychiatric effects to chronic alcoholism. Nystagmus, ataxia, tremor and slurred speech is frequently found. The most common mental symptoms are memory impairment, loss of orientation and depression or hypomania.[7,8]

When a person who has been habituated to large doses of barbiturates is abruptly deaddicted, psychotic behavior or convulsions may develop.[9,10] Such effects appear to result from an acquired chemical dependency of nerve cells to the presence of barbituric acid. These complications will be prevented by gradually decreasing the dosage of barbiturates.

This phenomenon has been utilized in reverse for the treatment of some cases of severe psychosomatic diseases.[11] Stupor-producing quantities of amobarbital are given for over a week. The medication is then suddenly withheld and a delirious reaction induced. Heldt believes that the abreaction during the delirium releases suppressed emotions which cannot otherwise be ventilated.

Opium Derivatives and the Synthetic Narcotics. Like the barbiturates, therapeutic amounts of the opiates can induce a delirium when an idiosyncrasy to these drugs is present. When anoxemia pre-exists, morphine will accentuate cerebral anoxia by depressing the respiratory center. Patients with congestive heart failure, shock or chronic cor pulmonale, for example, may become confused by small amounts of these narcotics. Since the opium alkaloids are conjugated in the liver, serious damage to this organ will prevent inactivation.[12] A typical toxic delirium was observed in a cirrhotic patient who received 10 mg. of morphine sulfate for right upper quadrant pain. He regained his mental clarity after forty-eight hours of vigorous treatment.

A delirium may occur as part of a severe withdrawal reaction. The abstinence syndrome seems to consist of a profound autonomic discharge, predominantly of the parasympathetic outflow tracts. In a debilitated addict the sweating, diarrhea, vomiting and insomnia can quickly lead to exhaustion. However, when a delirium occurs it is not due solely to the exhaustion state. There must also be an intimate affinity for the narcotic drug, for a small dose will usually clear the sensorium.

Bromides. Bromide intoxication is still so common that some neuropsychiatric hospitals do routine blood bromide determinations on all admissions.[13] Many physicians never recognize such cases, possibly because they are not aware of the obscure neurologic and psychiatric syndromes which bromism can evoke. Bromides have displaced barbiturates as the easiest sedatives to purchase. To people in chronic pain, in the tense and the distraught, bromides and alco-

hol are the last legal refuges. When they take too much bromides for too long they come afoul of the cumulative tendency of these salts.[14–16]

A great variation in sensitivity to bromide intoxication exists. Aged and unstable patients can develop mental disturbances at blood levels above 100 mg./100 cc. More resistant individuals seem to tolerate 200 mg./100 cc. or more without difficulty. No correlation exists between the bromide rash and the nervous symptoms. Overdosage is evidenced by weakness, insomnia, headache and confusion. These are often the very reasons why bromides were originally taken. Thus a vicious cycle of increased drug intake, followed by increased distress, is established.

A noteworthy feature of bromide psychosis is the great diversity of its manifestations. We have seen stupor, delirium, hallucinosis, paranoid states and Korsakoff syndromes. Some psychotic patients who recovered spontaneously after short periods of hospitalization may well have been aberrant cases of bromism.

Intake of chloride hastens the elimination of the bromide ion. One or two liters of normal saline daily will promote bromide excretion. Ammonium chloride is used when low sodium regimens are required. There is an unexplained lag between the reduction of the blood bromide level and clinical recovery.

Insulin. Insulin acts to make glucose intracellular, either by encouraging phosphorylation or by assisting in its transit across the cellular interface.[17] Since the neurone does not store glucose to any extent, and with the loss of sugar from the extracellular compartments during excessive insulin intake, brain cell glycopenia results. There is only a fair correlation between blood sugar determination and mental status. Other factors, including the rate of fall of the blood glucose level, contribute to the symptomatology.

Autonomic disturbances, such as profuse sweating, pallor or flushing, salivation and tachycardia, occur early. The first mental signs of hyperinsulinism are those of cortical strip glycopenia. Emotional instability, impaired mentation, somnolence, disorientation or mania may be seen. With involvement of the lower centers a deepening coma displaces the psychosis. During recovery the patient may again go through a delirious phase.

Prolonged hypoglycemia will irreversibly damage the brain cell. Re-establishment of a normal blood sugar range after many hours or days need not be accompanied by reversal of the neuropsychiatric derangements.[18] Two patients rescued from prolonged coma in the course of insulin coma therapy manifested permanent behavior forms reminiscent of lobotomized individuals.

Thiamine Deficiency. A deficiency of cocarboxylase, a thiamine derivative, results in derangements of carbohydrate enzyme systems. Nerve cell damage follows, but delirium is a relatively late manifestation. In this country it is seen in the malnutrition of chronic alcoholics who not only ingest less thiamine but who also require more for the catabolism of alcohol. The mental symptoms noted during thyrotoxicosis and other hypermetabolic states may relate to an increased thiamine requirement. When ocular palsies and ataxias are associated with the clouding of consciousness, the syndrome is named for Wernicke. The peripheral neuropathy, memory gaps and confabulation seen in Korsakoff's syndrome may originate in a cocarboxylase deficit.

Nicotinic Acid Deficiency. Nicotinic acid enters into carbohydrate utilization as a respiratory coenzyme. The psychosis associated with pellagra is well known but some of the precursor conditions are not always identified. The earlier symptoms are called neurasthenia and include such non-specific complaints as weakness, anorexia and irritability. Serious delirium can exist without the classic rash and gastrointestinal changes. Food faddists, alcoholics and the indigent are those most likely to be depleted of nicotinic acid. Cogwheel rigidity, grasp and sucking reflexes are more frequently seen in pellagrins than in any other type of delirium.

It is Forster's[19] impression that liver damage is a common denominator in many of the toxic psychoses. The hepatic dysfunction arises from a lack of nicotinic acid and causes the mental symptoms. His patients improved on nicotinamide but it must be pointed out that they had general supportive care sufficient to achieve recovery without attributing the results specifically to vitamin B_6.

ACTH and Cortisone. The psychiatric complications of cortisone or corticotrophin therapy are: dissociation of mood, breakdown into a neurosis and breakdown into a psychosis. The first of these is relatively harmless, although the impaired judgment associated with euphoria may have serious social or economic consequences.

One of our patients on cortisone lost several thousand dollars on a "deal" conceived and executed during a period of elation. The factors involved in cortisone euphoria are many, including the relief of chronic pain, the reprieve from invalidism, the loss of systemic toxicity and metabolic shifts within the brain cell. Neurotic breaks, with the onset of obsessive thinking, anxieties or phobias are not uncommon. Catatonic, paranoid or manic psychoses have been seen by us and described in the literature.[20]

It would be interesting to know the precise cause of these emotional changes. Many of the biochemical sequelae of corticosteroid therapy affect the neurone. Hypokalemia, alkalosis, sodium and water retention, sudden hypertension, abnormalities of carbohydrate and nitrogen metabolism are some of the deviations that could cause psychic side reactions. An abrupt metabolic shift, even in the direction of normal, may act as a stress.

Ransohoff and his group[21] believe that they have terminated psychotic episodes in two patients using supplementary potassium. In a discussion of this paper Glaser states that there is no obvious relationship between psychotic reactions during ACTH therapy and the serum potassium level or EEG changes. Our conclusion has been that local sodium and water retention in the brain may play a part. This can occur in the absence of manifest peripheral edema. We have followed one patient with subacute lymphatic leukemia who was kept on cortisone and ACTH despite a mixed psychosis and convulsions. His resting spinal fluid pressure was found to be 480 mm. of water. After this pressure was carefully reduced to 300 mm. he became accessible and coherent for about four hours. He then reverted to a catatonic-like state with echolalia and waxy flexibility. Each reduction in cerebrospinal fluid pressure would produce a temporary improvement. The hematologic remission persisted but the mental picture varied widely from complete lucidity to irrationality, mutism and paranoid frenzy. It was interesting to observe that during the last week of this patient's life his psychosis abated. This transpired in spite of continuing ACTH-cortisone injections, a nocardial septicemia and exacerbation of his leukemia.

The factors resulting in psychobiologic stress during ACTH-cortisone treatment have been enumerated by Rome and Braceland:[22] (1) The sudden improvement of a chronic illness may find the patient unprepared to relinquish the advantages of being ill or to accept the responsibilities of being well. (2) Steroids seem to release occult emotional energies which are ordinarily repressed. (3) The distortions of face and figure of a Cushing-like syndrome may depress some patients. (4) Withdrawal of cortisone produces a temporary addisonian state due to the suppression of intrinsic adrenal-cortical secretion. (5) The patient may be emotionally unprepared for the exacerbation of the illness after the treatment is discontinued.

These forces, and the many biochemical effects, can alter psychic homeostasis. The problem is so complex that Clark[23] could find no interrelation between the development of psychotic behavior and the dose of the drug, the therapeutic response or the blood chemistry findings. Nor does Romanshoff[21] subscribe to the opinion that patients can be psychologically screened so that major mental complications to therapy will be avoided. We have given cortisone and its trophic hormone in full doses to a number of severely neurotic and psychotic patients. It has been rare to witness any profound change in their individual reaction patterns. Perhaps it is those persons who have poorly developed defenses against anxiety who experience the major mental changes from these hormones. Whether these defenses are of the normal, neurotic or psychotic variety may be immaterial.

Digitalis. Digitalis delirium is rare but proven cases are recorded in the literature.[24] Ordinarily, the part played by digitalis as a deliriant agent is not easy to evaluate since it is used in patients hypoxic from their heart failure and receiving other medicines.

It becomes suspect when mental confusion appears in spite of improving cardiac function. If the delirium recedes after stopping digitalis and recurs after restarting the drug, a causal relationship could be assumed. When the mental changes occur shortly after a copious diuresis, it is supposedly due to abrupt electrolyte shifts.

Psychoses can appear well within the therapeutic dose range; nor does the use of the glucosides diminish their incidence. An important clinical decision must be made when a patient on digitalis becomes disoriented. The question of withholding the drug and decreasing cardiac efficiency, or continuing the digitalis and perpetuating the psychosis arises. Fortunately, we are now able to treat congestive heart failure satisfactorily with mercurial diuretics, low salt

diet and ion exchange resins when digitalis becomes contraindicated.

Atabrine. In his presentation of the atabrine psychoses Grieber[25] found two basic mechanisms for these reactions. Atabrine can unleash a psychosis in predisposed persons who were experiencing either an emotional upheaval or an acute illness. Drug sensitivity was suspected when stable personalities broke down on atabrine. Retesting of these people after recovery produced recurrences.

Both suppressive and therapeutic amounts of this drug were psychotogenic. The onset was explosive and all varieties of psychiatric syndromes were observed. The psychosis cleared within a month of abstinence from atabrine. When malaria is present, another potential cause of encephalopathic disturbances coexists.

Other Drugs. The case reports of psychoses in amphetamine[26–28] and marihuana users[29] almost invariably concern persons of unstable prepsychotic personality. Review of their history indicates that the drugs usually released a latent psychopathy and were not truly toxic in origin.

Mescaline[30] and lysergic acid diethylamide[31,32] will effect a transient psychosis in all subjects. These substances are of interest because they produce a picture resembling schizophrenia. Euphoria, depersonalization, slowing of time perception and vividly colored hallucinations can be induced with minute dosages.

Other drugs which have been associated with psychotic reactions are the antihistaminics,[33–36] the sulfonamides,[37] DDT,[38] lead,[39] cocaine,[40] thiocyanate,[41,42] carbon monoxide,[43] the hydrazines of isonicotinic acid,[44] the nitrogen mustards[45] and atropine and related compounds.[46,47]

ENDOGENOUS FACTORS CAPABLE OF PRODUCING A PSYCHOSIS

The Anemias. Sudden, copious blood loss is closely associated with delirium or syncope. These symptoms may be attributed to diminished cerebral blood flow and consequent hypoxia of the brain. Gradual blood loss is counterbalanced by vascular mechanisms which give preferential treatment to the cerebral blood supply. Eventually these also fail, with resultant psychic decompensation. With timely restitution of blood volume and arterial pressure the psychosis subsides. Morphine, a standard drug in the treatment of hemorrhage, can contribute to the confusional state. This is illustrated by a seventy-five year old patient with hematemesis and melena from a bleeding gastric ulcer who was given morphine before transportation to the hospital. He arrived in a roaring drunk trying to escape from Cecil, the television sea serpent.

In the primary anemias insufficient hemoglobin for adequate oxygen transport likewise causes loss of mental compensation. We have followed two patients with pernicious anemia whose psychoses had a paranoid flavor. One was a forty-five year old, blue-eyed, gray-haired woman admitted with a diagnosis of "involutional paranoid psychosis." Laboratory and clinical data were typical of pernicious anemia with subacute combined degeneration of the cord. She was so noisy and destructive that almost continuous tepid tubs were required. Complete hematologic and mental recovery occurred on vitamin B_{12} injections, but with incomplete neurologic remission. In a Mexican male of thirty-three, three distinct psychotic breakdowns were witnessed because of lapses in treatment of his pernicious anemia. During each recurrence he was suspicious, fearful, seclusive, and thought that the doctors were plotting to destroy him. After treatment with refined liver he was apologetic of his behavior and aware that he had been delusional. In this patient it was possible to correlate the hemoglobin level with the psychic undulations.

Addison's Disease. Cerebral metabolism is unfavorably influenced by many components of the addisonian state. Brain cell nutrition is impaired by the hypotension, hypometabolism, hypoglycemia and the shrinkage of blood volume. Ordinarily, the patient in adrenal-cortical crisis is rational but a delirium based on accentuation of the metabolic deviations mentioned can evolve. Depressive and paranoid reactions are most common in hypoadrenalism. Prompt treatment with glucose, saline, cortisone and DOCA will restore mental clarity; procrastination can result in a fixed psychosis.

Gorman and Wortis[48] point out that Addison's disease, like any other chronic, debilitating illness, can eventuate in dissolution of the ego. Invalidism is a serious emotional stress which will overwhelm an occasional individual who cannot accept the idea of permanent disability.

Cushing's Syndrome. The psychologic consequences of excessive circulating adrenal-cortical steroids have been considered. Sporadic case reports of mental disturbances during Cushing's syndrome have appeared.[49] In our case[50] a basophilic adenoma of the pituitary was present

for at least five years before delusions of being God's spokesman, paranoid refusal to eat because the food was poisoned, hyperactivity and loss of orientation developed. After three months these mental symptoms remitted spontaneously and never recurred. Psychotic depression has been a prominent feature of other cases.[51]

An incidental psychosis in a rare disease seems of no great significance. However, to those who believe that psychic, like physical stress, is mediated through the hypothalamic-pituitary-adrenal-cortical axis the psychoses of Addison's and Cushing's diseases are engrossing. There is still no good proof that psychologic breakdowns are comparable to Selye's "stage of exhaustion" which he has postulated for certain diseases of adaptation.[52]

Hypoparathyroidism. We have seen three types of mental abnormality in connection with failure of the parathyroid glands. These were a toxic psychosis ascribed to shifts in serum calcium and phosphorus, irreversible mental deterioration from long-standing hypocalcemia, and release of a schizophrenic process by uncontrolled hypoparathyroidism.

Slowly progressive brain damage is acquired when the condition is untreated for many years. In one such case, recurrent, atypical "convulsions" and bilateral cataracts in a young man finally resulted in a determination of the serum calcium and phosphorus. When hypocalcemia and hyperphosphatemia were found dihydrotachysterol was administered and effected a return of these electrolytes to normal. The hypocalcemia and hyperphosphatemia have been corrected for over three years but there is only partial improvement in intelligence on serial psychometric testing.

The case of a man with familial, idiopathic hypoparathyroidism has been reported.[53] During his metabolic balance studies he became overtalkative, had flight of ideas and heard voices coming from the radiator. He did not improve in spite of adequate substitution therapy with dihydrotachysterol. Psychiatric evaluation indicated that the patient was a paranoid schizophrenic with manic features. A study of his past history and psychologic testing confirmed this diagnosis. Insulin coma therapy was only partially effective. The hypoparathyroidism was thought to be a precipitant of the psychosis.

A toxic delirium was reported in five of eighteen post-thyroidectomy hypoparathyroid patients by Greene and Swanson.[54] Within a week after surgery a delirious reaction was observed. There was full recovery in all five patients but it lagged behind the rise in serum calcium. After the initial episode delirium did not accompany the recurrence of tetany. This indicates that postoperative factors and loss of thyroid tissue could have contributed to the psychosis.

Hyperparathyroidism and Vitamin D Intoxication. Psychic changes are rare complications of hyperparathyroidism and vitamin D intoxication. The action of a high calcium ion concentration on the brain cell may explain the mental symptoms when they arise. At autopsy, minute, ectopic calcifications have been found in the nervous system. Similar deposits in the renal tubules eventually give rise to uremia with its mental changes.

The usual picture is that of a psychosis which subsides upon removal of the parathyroid adenoma. Fitz and Hallman[55] have described a patient who had markedly paranoid ideas without delirium. Headaches and dizziness existed since a depressed skull fracture fifteen years previously. The chief complaints consisted of epigastric and right lower abdominal pain, urinary frequency, burning and dribbling. No bone lesions were found. The serum calcium was 14 mg. per cent. After removal of the parathyroid tumor the calcium dropped to 10 mg. per cent and there was complete recovery from the psychosis.

Hypothyroidism. Myxedematous madness, as Asher[56] prefers to call it, is a little known and less frequently recognized entity. The psychosis may be part of an easily identified hypothyroidism, or it may overshadow all other symptoms of the disease. Nor do the mental deviations necessarily reflect the hypometabolic state. Maniacal reactions are seen as often as apathy, mental torpor and depression. In post-thyroidectomy psychoses the premorbid personality has frequently been noted to be of a compulsive type with cyclic mood swings.[57] Asher reemphasizes that there is no specific myxedematous type of psychosis but that the diagnosis must be made on physical examination and laboratory data. He believes that a survey of mental institutions would reveal an occasional hypothyroid patient masquerading as a functional psychotic. These people might still be helped with thyroid extract.

The presence of hypothyroidism and mental disease in a patient may be fortuitous or of etiologic significance. It should also be kept in

mind that long-standing catatonia can reduce thyroid activity as measured by radioiodine uptake studies. This is probably a reflection of a widespread endocrine involution.

Thyrotoxicosis. There are sound theoretic reasons why the patient with hyperthyroidism may experience mental complications. The hypermetabolism results in an increased cellular oxygen requirement. McGavack[58] states that the excessive amounts of circulating thyroxin and epinephrine-like substances adversely affect the central nervous system. He subscribes to the belief that liver failure in thyrotoxicosis can be responsible for the toxic psychosis. When the heart fails, the oxygen deficit increases.

A classic delirium can give way in thyroid crises to uncontrollable laughter or tears, mania and finally coma. The management of the thyrotoxic psychosis should be directed toward quick reduction of the excessive thyroid secretion. Iodine will produce this effect most rapidly. Operation prior to such treatment is contraindicated.

Graves' disease enters into the differential diagnosis of some psychiatric conditions. The patient in an anxiety neurosis has a tremor, perspires excessively, has a staring expression, a rapid heart action and complains of diarrhea. He may show other signs of sympathetic overstimulation. Hyperthyroidism can also be simulated by someone in an agitated depression. Here the weight loss, the facies and the incessant motor activity are reminiscent of thyrotoxicosis.

Heart Disease. It is a not uncommon experience to have a patient with severe congestive heart failure or myocardial infarction become delirious. The onset is gradual with increasing restlessness, irritability and a dulled sensorium. The altered dynamics of cardiac insufficiency definitely affect mental function.[59] Pulmonary edema and arteriovenous shunts lead to impaired arterial oxygenation. Venous and capillary engorgement and diminished blood flow make the exchange of metabolites inefficient. Collapse of the peripheral circulation adds to the cerebral anemia.

Anxiety and emotional instability have often been noted in connection with chronic heart disease. Cardiac failure and infarction are heavily medicated illnesses, each drug being a potential toxin. Endogenous poisons are elaborated during the late stages of cardiovascular disease when uremia and renal acidosis arise.

One of the saddest sights in medical practice is the terminal cardiac patient who has outlived his cerebral circulation. To the anguish of his friends and family he becomes violently paranoid and is relegated to a psychiatric ward to spend his last days.

Fever. The central nervous system is sensitive to sudden temperature elevations. The child tends to respond to hyperthermia with convulsions, the adult with a delirium. We no longer see the mental aberrations of lobar pneumonia or typhoid fever which our predecessors described since these infectious diseases have been controlled by the antibiotics.

An instructive example of the effect of fever was in a thirty-eight year old male with sinusitis and a respiratory infection complicated by an iliofemoral thrombophlebitis. His excited confusion continued for weeks and was interspersed with lucid intervals. Delusions that he had killed his mother and father were expressed. He lapsed into a mute state and was given an amobarbital interview during which he was in contact and responded rationally to questioning. After six electroshock treatments a complete remission developed. Psychologic and psychiatric evaluation after recovery revealed no evidence of schizophrenic trends. A history of a delirious reaction to every febrile illness since childhood was elicited after recovery.

Renal Insufficiency. We anticipate drowsiness, coma and convulsions during uremia but at times the psychiatric disturbances will mask the entire clinical picture. A young man was admitted to the Neuropsychiatric Hospital with a diagnosis of paranoid schizophrenia. It was only because of his "cafe au lait" complexion and the trace of albumin in his urine that a blood urea nitrogen was requested. This was reported as 232 mg. per cent. At autopsy, bilateral congenitally hypoplastic kidneys were found.

The precise waste product that engenders uremic symptoms is not known. It is not urea, creatinine or any of the substances which we use to measure nitrogen retention. The uremic psychosis may mimic any of the known functional psychoses.[60] Although it is usually a terminal expression of kidney failure, unpredictable lucid intervals can occur.

Liver Disease. It is to be expected that liver disease will be complicated by neuropsychiatric aberrations. Functional liver tissue detoxifies and excretes many of the endogenous and exogenous poisons. When liver damage is present, these substances are recirculated, to the detriment of the nerve cell. The overwhelming

effect of modest doses of the rapidly acting barbiturates on cirrhotics has already been mentioned.

In various forms of leptospirosis, delirium is not uncommon because liver damage, spiking temperatures and severe infection coexist. Furthermore, leptospirosis and other infectious liver diseases have a predeliction for involvement of the brain and its coverings.

The opinion has been offered[61] that the brain cell changes in Wilson's disease are the result of hepatic insufficiency. Undetoxified metabolites, acting over long periods, together with loss of amino acids, are said to effect demyelinization of the basal ganglia and cortical cells. Similar microscopic findings have been demonstrated in chronic hepatitis.

Mental depression and retardation is a feature of acute viral hepatitis but delirium is infrequent. In cirrhosis the alcoholism, avitaminosis, malnutrition and liver dysfunction are so intertwined that an evaluation of the exact cause of the delirium is hardly possible.

Hepatic coma is supposedly provoked by the autolytic products of massive liver necrosis. Lethargy, delirium and convulsions usher in the final stupor but even at this point an occasional patient may be salvaged with vigorous treatment.

Postoperative and Postpartum Psychoses. All the factors favoring the development of a toxic psychosis may be present in the postoperative and puerperal state. The summation of blood loss with hypotension, infection, pain, tissue trauma, exhaustion and nutritional imbalance can upset psychic equilibrium. Anesthetics and postoperative sedation may be contributory. The patient's fear of death and mutilation, the unfamiliar surroundings, the impersonality of some surgeons, are more subtle but nonetheless important considerations.

An average of one psychosis following every 400 operations has been recorded.[62] As geriatric surgery increases, more postoperative deliria will occur.[63] We have noticed that cataract operations result in a high proportion of mental disturbances. Perhaps the long postoperative period, during which the eyes are covered, preventing visual orientation, is conducive to delirium.

Much can be done to avoid these psychic derangements. A genuine interest in the patient, not merely his removable viscera, is desirable. Inquiring into, and allaying his fears, would be a worth while project. Quick restitution of his abnormal electrolyte imbalance, and avoidance of oversedation following surgery, are obvious requisites.

Postpartum delirium may be the result of a multiplicity of coalescing causes. In addition to those mentioned above, unconscious motives may play a part. The following have been found to be important concealed emotional factors in puerperal psychoses: terror of maternal responsibilities, unresolved conflicts of a childhood jealousy, unacknowledged resistance against resuming unacceptable marital relationships, or a panic reaction because of shamefully erotic feelings which the patient has toward the obstetrician or nurse.[64]

Multiple Causes for Delirium. Normally, in our cases of toxic delirium it has been possible to discern a major and several lesser reasons for the disturbance. In some instances it was quite impossible to designate a prime factor but a number of causes could be named. We have been impressed in our review of this subject by the plurality, rather than the unity, of etiology.

In an anemic, malnourished, feverish and dehydrated fifty-six year old man with an inoperable carcinoma of the hypopharynx, disorientation, agitation and depression developed. He was receiving large doses of codeine for pain, and atropine to diminish oral secretions which he could not swallow. The precarious economic family situation and his painful and critical illness were the obvious causes of his depression. He became alert and cooperative after a gastrostomy tube was placed and the codeine was reduced. We do not think of this event as a codeine delirium but consider that multiple factors played equally important roles.

A young man, who had been a problem drinker, became restless, destructive and noisy one week after operation for a gangrenous appendix which ruptured during operation. He was receiving secobarbital, penicillin and streptomycin. The sedative was immediately under suspicion but the next day a generalized urticaria was manifest. The patient was later found to be sensitive to penicillin. Did he have angioneurotic edema of the brain from the penicillin,[65] delirium tremens, barbiturate intoxication or a combination of these?

RELATIONSHIPS BETWEEN A TOXIN AND A PSYCHOSIS

When the administration of a drug is followed by the onset of mental changes, a simple cause

and effect connection should not invariably be assumed.[61] There are a variety of possible correlations between the development of a psychosis in the presence of a noxious agent:

1. There may be only a coincidental relation between the toxin and the psychosis. Schizophrenia and manic depressive psychoses are lifelong, often intermittent, illnesses. Such people will also have many physical ailments and many drugs administered during their lifetime. We might consider that these intercurrent events are the source of the psychosis when actually we are observing the natural fluctuations of the mental illness.

2. The toxic agent acts as a trigger to release a personality disturbance latent within the individual. A drug or an illness may act as a stress sufficient to topple a previously unstable emotional structure. Some cases of toxic psychoses which do not clear on adequate treatment fall into this category.

3. The toxin directly causes the psychosis by its adverse effect on brain cell metabolism. There may be minor contributory psychologic and physiologic factors but the specific toxin plays the dominant role.

4. The psychosis can emerge after successful treatment of a psychosomatic disease such as peptic ulcer.[66] It may be assumed in such cases that the illness was a necessary defense which maintained the patient's borderline adjustment to his environment. If no substitute psychologic support is available after the disease is cured, the internal conflicts may erupt into an acute psychosis.

5. Withdrawal of some drugs can provoke a psychic crisis. Two possible mechanisms may mediate this sequence of events. The organism could have become physiologically adapted to the presence of the drug in the tissues. Sudden discontinuance may prove to be a serious strain. A number of the withdrawal psychoses of narcotic addicts fall into this class. A second group consists of marginal psychotics who maintain compensation with alcohol or sedatives. Abrupt loss of this support demolishes their fragile defenses.

6. The absence of some metabolite necessary for brain cell function may effect a psychosis. Brain cell metabolism depends preponderantly on glucose, oxygen and certain factors in the vitamin B complex. Hypoglycemia, mountain sickness and pellagra are some obvious examples within this category.

That drug which is least familiar to the physician will invariably be blamed for the toxic psychosis. When a new medicine is introduced, it is commonly accused of all undesirable changes in the patient's condition. We overlook the fact that the old, reliable drugs and the disease process itself have unfavorable side effects. This situation was illustrated by a patient with an inoperable prostatic carcinoma who became disoriented and delusional. He was one of a group of patients undergoing investigation to determine the effects of large amounts of cortisone on cancer of the prostate. He received 1,000 mg. of cortone® daily; in addition, meperidine was administered for pain. It seemed obvious that the cortone was the offender but there was no improvement for two weeks after it was discontinued. It was then postulated that the psychosis was caused by a cerebral metastasis from the prostatic malignancy. However, within twenty-four hours after the meperidine had been omitted the patient made a complete recovery from his delirium.

DIAGNOSIS

If we could detect the earliest deviations from a patient's usual behavior, the difficulties in controlling a delirium in full swing might be avoided. The first symptoms of the impending mental disorganization are due to failure of the highest cortical functions, particularly of intelligence and emotional control. Judgment and abstract reasoning are impaired, attention wanders and recall is blurred. The ability to adjust to changing situations is diminished. During this predelirium diurnal restlessness and nocturnal insomnia emerge. The patient becomes petulant and vaguely apprehensive. An alert physician can detect these premonitory alterations by looking and listening for them. If this subtle transition in the patient's usual mood and attitude is disregarded, we are then confronted with "sudden" onset of confusion and disorientation.

Orientation in time is first to be lost, since it requires the most complex cerebration.[13] Awareness of place and situation is then lost, and thereafter awareness of self fades away. Illusions, or misinterpretations of sensory stimuli, are commonly noted, e.g. the noise of a dropped bedpan becomes a shot aimed at the patient. When such false impressions are structured into concepts, delusions are expressed. The content of these delusional fabrications are drawn from and colored by the hidden conflicts in the pa-

tient's personality. Hallucinations are most frequently visual or auditory, whereas false perceptions of smell, taste and touch are rare.

The hallucinatory and delusional material produced is by no means random or indeterminate. It is a distorted reflection of the person as he is, his life experiences and his hidden drives. The mood changes are determined by the release of suppressed emotional patterns. All of us carry an emotional load of concealed anxiety, guilt or depression. During a delirium these become evident as fear and suspicion, and usually are projected onto the attending personnel.

It is a matter of practical importance to understand that these delusory beliefs are very real to the person who has them. All but the most feeble can respond to their misconceptions. They can assault anyone whom they imagine to be a persecutor. They are capable of running away from tormentors through unprotected windows. Willful suicide is rare in toxic deliria but self destruction in response to a persecutory delusion certainly occurs.

One of the familiar symptoms of delirium is the fluctuating level of consciousness. It may vary, hour by hour, from overalertness to profound stupor, and is distinctly worse at night. This nocturnal worsening of the mental state has been pondered by many observers. It has been ascribed to the illusions which shadows and darkness generate. Even a normal person fantasies more readily in the dark; the delirious may lose whatever hold they have on reality when darkness blurs their visual perceptions. A diurnal variation in cerebrospinal fluid pressure has been demonstrated. It could be that concomitant changes in cerebral metabolism exist, accounting for these variations in the level of consciousness.

Transfer to a hospital has been found to release a delirium in someone verging on this condition.[67] Perhaps the additional burden of coping with an unfamiliar environment at a time when the mind is barely able to maintain a balance may be a decisive blow. The factor of abrupt drug withdrawal may also play a part in the onset of a delirium following hospitalization. Delirium tremens, for example, typically occurs during the sobering up stage. It can become manifest weeks, even months, after alcoholic intake has ceased. Usually it is unleashed by the stress of an infection, operation or trauma.

The appearance of the delirious patient is well known. He looks acutely ill, with flushed face and an anxious, sometimes desperate, expression. A coarse tremor is present, and picking movements are sometimes seen. Sweating is profuse, and hyperpnea and tachycardia are invariably noted. Usually the patient is febrile either as a result of his basic illness or secondary to dehydration. There are many causes of dehydration in this condition; fluid intake is poor, hyperactivity, peripheral vasodilation and fever increase water loss. In the elderly a "cold" delirium is sometimes observed. The patient is pale and cool, he lies quietly in bed, and his confusion is disclosed only by his response to questioning.

After recovery a memory gap for the delirious experience may remain. Only following a hallucinosis is remembrance of the experience evident. When fragments are remembered they are interpreted as nightmares. It is rare to find persistence in the belief that the hallucinatory episodes actually occurred. When full insight into the transient psychosis is not achieved, an underlying organic or functional psychosis may have coexisted.

It is often possible to reproduce the psychosis with the same toxic substance after recovery. The dosage required may be remarkably constant. We have followed a Mexican male with pernicious anemia who would become delusional whenever his hemoglobin fell below 4.0 gm. per 100 cc. Another patient had two cataract operations, one in 1943, the second in 1951. On both occasions he received small amounts of barbiturates for premedication. In both instances a delirium ensued with a peculiarly similar content. Ordinarily, however, the patient cannot be titrated against the drug because of the multitude of varying factors which determine the psychotogenic threshold at any moment.

GROUPS WITH A LOWERED THRESHOLD TO DELIRIUM

The elderly patient is particularly susceptible to delirious reactions.[68] There are a number of contributory factors to this predisposition. A diminished cerebral blood flow, and the degenerative changes within the cortical neurones are the physiopathologic components. With increasing age sensory perception becomes poorer. The personality congeals and cannot adjust to stresses as in youth. The fears and insecurities of old age tend to lessen psychic stability to a

precarious level. Drugs, especially sedatives, then act as the final insult and topple the senile patient into a delirium. A fifth of the psychoses of old age are toxic; in another fifth a toxin contributes to the breakdown.[69]

Another group which has a lowered tolerance to cerebral toxins comprises people with previous brain damage. A thirty year old man with post-traumatic epilepsy became ill with a bronchopneumonia. Although the temperature never exceeded 102°F. and subsided within twenty-four hours, he was completely disoriented for six days. Another patient who had an encephalitis four years previously developed a severe delirium in conjunction with an ordinary bout of acute tonsillitis. The infection responded promptly to antibiotics but the mental confusion persisted for a week. It is a common experience that the alcoholic who suffers a serious head injury loses his capacity for drink. One drink might result in the same degree of befuddlement that a bottle of whiskey had previously generated.

People in severe pain can become subject to brief psychotic reactions when sedatives rather than analgesics are administered. The sedative does not sedate, but instead diminishes the restraining influence of the higher centers on the person's behavior. The response to continuing pain becomes a primitive one. These patients may become noisy, violent and completely uncooperative. For example, such chaotic situations are not uncommon when women in active labor are given small doses of barbiturates.

Finally, a moribund patient may go through a phase of confused excitement before the terminal coma arrives. This is a reflection of the increasing cerebral anoxia which is engulfing the patient.

DIFFERENTIAL DIAGNOSIS

A patient seen initially during an acute psychotic reaction poses a difficult diagnostic problem. There are a substantial number of internal and external toxic agents to be considered, and rarely do any produce a clinical picture typical for the specific intoxicant. These substances can release mental symptoms closely resembling the functional psychoses. Sometimes it is impossible to make an immediate differentiation; a study of the psychiatric history and the evolution of the disease becomes necessary. Examination of the delusional material and behavior may be rewarding.[70] The delirious person mistakes the unfamiliar for the familiar, his hallucinations are homely and may refer back to his occupation or home life. The schizophrenic in delirium mistakes the familiar for the unfamiliar, his fantasies are bizarre, remote and obscure. In a toxic delirium the disorientation usually exceeds that found in the functional psychoses. The wild agitation and violent destructiveness of the manic, acute catatonic excitement, and the toxic delirious state can be initially undistinguishable.

A differentiation must be made from those disorders that produce psychotic changes secondary to gross brain damage. A space occupying lesion may present as a fulminating psychosis. Cerebrovascular disease can give rise to delirial patterns. Inflammatory processes within the cranial vault are often associated with temporary personality deviations and confusional episodes. There are also a large number of systemic illnesses which affect cerebral function. This group includes the collagen[71] and rickettsial diseases,[72] thromboangiitis obliterans,[73] trichinosis,[74] malignant hypertension,[75] thrombotic thrombocytopenic purpura,[76] infectious mononucleosis,[77] the lymphomas[78] and others.

PROGNOSIS

In general the prognosis of the exogenous psychoses is favorable, providing the offending agent can be eliminated in time to prevent irrevocable changes. A patient in a delirium is in the equivalent of the second stage of anesthesia. It is the patient in the fourth stage, or coma, who has had a more overwhelming exposure to the intoxicant and whose condition is more precarious. The biochemical changes are reversible up to a point beyond which permanent brain damage with mental deterioration or chronic psychosis occurs.

In the endogenous toxic psychoses the outlook depends on the underlying disease with the qualification that the interposition of a psychosis indicates either a severe form of the disease or a predisposition of the patient to become and remain psychotic.

Perhaps the favorable prognosis in the toxic psychoses is a semantic deception. When the disturbance becomes chronic, the diagnosis is often changed to "cerebral arteriosclerosis with psychosis" in the old, and "schizophrenic reaction" in the young. Without question cerebrovascular insufficiency and schizophrenia can be made manifest by a cerebral toxin, but cases of chronic psychosis entirely due to pro-

longed or intensive exposure to a toxin are also seen.

There is a mortality directly related to the delirious state. We have mentioned the possibility of a patient destroying himself in response to a delusion. A continuing delirium can be fatal from exhaustion, peripheral collapse and aspiration pneumonia.

PROPHYLAXIS

Serious consideration should be given to the prevention of delirium due to a major illness or drug therapy.[79] The following is a check list for the avoidance of toxic mental complications: (1) Consider the patient and his fears. (2) Distrust all medicines when predelirium occurs. (3) Combat anemia and poor oxygen exchange. (4) Secure sleep and rest. (5) Avoid deliriant drugs if possible. (6) Maintain nutrition. (7) Reduce hyperpyrexia. (8) Control hormonal, vitamin, electrolyte and fluid imbalance. (9) Support cardiorenal function.

TREATMENT

There are a number of general principles which can be formulated for management of the toxic psychoses. These are the groundwork upon which individualization of treatment, depending on the distinctive clinical picture, should rest.

Detoxification. The toxin must be recognized and eliminated or neutralized if possible. Abrupt discontinuance of the drug is preferable but there are conditions when tapering off will be more prudent. Narcotic and barbiturate addicts can become critically ill from sudden stoppage of their medication. On the other hand, the alcoholic can be rapidly detoxified if he remains under observation.

When a deficiency psychosis exists, the missing factor must be discovered and supplied. The search for the psychotogenic agent can be extraordinarily complicated. A reliable history usually cannot be obtained. The physical examination is performed on a patient who is less than cooperative. The presence of serious physical disease treated with many drugs will require unraveling to disclose whether the disease or the drugs caused the intercurrent delirium.

Nutrition. Food, fluids, electrolytes and vitamins must be supplied according to need. The negative nitrogen balance of any prolonged or hectic illness is increased by the hyperactivity of the disturbed patient. Somehow, caloric and protein loss must be reduced. Food by mouth, usually in the form of high caloric liquids, should be urged. At times the patient will be unwilling to eat. One of the notable features of the delirium is the suggestibility of the patient. This characteristic should be manipulated in a positive manner to produce an adequate food intake.

Gastric tube feeding is an undesirable and sometimes dangerous procedure in the noncooperative patient. Vomiting and aspiration of the instilled contents may occur. What the forceful induction of a gastric tube represents to a psychotic person is worthy of some reflection.

When parenteral fluids are necessary, hypodermoclyses with hyaluronidase will allow sufficient fluid intake and still permit some freedom of movement. If intravenous feedings are selected, the extremity and the needle must be well secured and watched.

The need for water and salts is even greater than for food. Dehydration and salt loss is invariable and compounds the brain's metabolic imbalance. Correction of these deficits must be made with care when renal or cardiac function is impaired.

During the initial phases of a delirium there is poor vitamin intake and increased utilization from the hypermetabolic effects of fever and agitation. It is customary to give large quantities of the water-soluble vitamins in the hope that the cellular enzymatic reactions will proceed at an optimal rate. Although we are aware that the bulk of the parenterally administered water-soluble vitamins are excreted in the urine, we have continued the common practice of flooding the body with large quantities of vitamin B complex and ascorbic acid.

Oxygen. Cerebral anoxia plays a cardinal role in many delirial reactions. Oxygen therapy is indicated whenever cyanosis, pallor or dyspnea appears. Unfortunately, the irrational patient tends to interpret a mask as a threat to suffocate him. The tent may represent a lethal chamber, and the catheter might be a snake. Unless the use of oxygen is made acceptable the fears engendered by its use will outweigh its beneficial effects. The need for supervision of the patient under oxygen is obvious.

Paradoxically, in chronic lung disease oxygen therapy can produce delirium or coma.[80,81] When oxygen in high concentration is administered, the respiratory rate decreases, and carbon dioxide narcosis and respiratory acidosis ensues.

This mechanism should be considered when a patient with advanced emphysema or fibrosis becomes worse after oxygen has been started.

Nursing Care. The understanding and skillful nurse is a most important factor in recovery. She is aware that her patient is deeply troubled by his fantasies and is fearful, distrustful and bewildered. This knowledge permits the nurse to comprehend his strange behavior, accept his threats, ignore his insults and prevail upon him to take nourishment and treatment. Each nursing procedure should be explained simply, even when it appears unlikely that the patient can grasp one's meaning. As a rule he is more aware of what is transpiring than we believe. It is a breach of good nursing to make provocative or facetious comments within the patient's hearing. It is part of his illness for him to extract fragments from his surroundings and incorporate them into a persecutory system.

Whenever possible the actively delirious patient should be under observation. Not only will accidents be prevented but also the patient will derive comfort when someone is close. A quiet member of the family, toward whom the patient is not antagonistic at the moment, can be used as a sitter. Some obtain solace from having their hands held or stroked. That such elemental physical contact gives reassurance is a measure of the regression that has occurred.

The room should be light and quiet to reduce the number of illusion-producing stimuli. Just as prolonged recumbency has been reported to produce a delirium,[6,82] the assumption of a sitting position might restore mental clarity in the disoriented. This is not because cerebral oxygen utilization is increased in the upright posture. If improvement occurs it may be attributed to improved aeration of the lungs, or to the return of the patient to a more familiar perspective.

Psychiatric Care. In a deranged patient attitudes replace words as the prime means of influencing his conduct. A calm and accepting appearance on the part of all the personnel will sometimes be transmitted to the patient; if not, it will at least soothe the relatives.

Should an attempt be made to argue the patient out of his delusions? A striking lack of success will reward the logical approach. He will merely become suspicious of the doctor's or nurse's motives. Yet, to agree with the paranoidal beliefs might reinforce them. The best attitude seems to be one of neutrality. While the patient is recovering, the discrepancy between his erroneous interpretations and reality should be pointed out gently.

There appears to be no possibility of using conventional psychiatric technics with a delirious subject. Valuable information may be obtained from the hallucinatory material but little practical use can be made of it at a time when it is most needed.

Sedation and Restraints. The best device for achieving rest is the tepid tub maintained at a temperature of 95–100°F. This simple hydrotherapeutic measure is available in the home as well as in the hospital. With someone in attendance the tub can be used for hours and the degree of relaxation is gratifying. Neutral packs, in which the patient is wrapped in cool, wet sheets, are also restful, except for the occasional one who "fights the sheets." During both procedures it is common for the patient to go to sleep.

Under ideal conditions the use of chemical or mechanical restraints would never be used on the acutely psychotic. Practically, these measures are necessary at times. The problem of sedatives is a difficult one. The disadvantage of sleepless excitement must be weighed against the disadvantage of adding another potentially toxic chemical.

The least deliriant of the hypnotics is paraldehyde. In adequate dosage it produces quick sleep and has a wide margin of safety. Fifteen cubic centimeters can be given in fruit juice or compound spirit of orange and repeated if necessary. The odor and taste are objectionable and it is a gastrointestinal irritant. For those who cannot or will not tolerate the drug by mouth, it may be instilled rectally as a 10 per cent retention enema in saline. This route of administration will not have wide application since confused patients cannot cooperate sufficiently, nor is rectal medication advisable from the psychiatric viewpoint. The intramuscular route is safe, providing a large calibre needle is placed deep into the muscle, and the injection is made slowly. Sterile abscesses can form from forceful instillation of paraldehyde into fatty tissue. Intravenous injection must be made slowly so that the cough reflex is not activated. Five or ten cubic centimeters can be put in 1 L. of glucose solution for intravenous drip use. The gradient of falling asleep and awakening appears to be steeper with paraldehyde than with other sedatives. Less time is spent in a drowsy, semi-

oriented state. This drug is widely used for acute alcoholism and delirium tremens. An occasional alcoholic will become addicted to the unconsciousness which paraldehyde offers unless it is tapered off within a few days.

Chloral hydrate brings a restful sleep and is only rarely the cause of undesirable reactions. Doses of 1 to 2 gm. are sufficient, but turbulent patients require more. In the elderly person with cerebral arteriosclerosis who becomes delirious from modest doses of barbiturates, chloral will induce a dreamless sleep. It is available in capsule form, or can be taken in a 25 per cent solution of peppermint water. Given over long periods chloral can also give rise to delirium.[83]

Intramuscular or intravenous amobarbital or secobarbital are sometimes necessary for the rapid sedation of a disturbed patient in whom paraldehyde is contraindicated. It is imperative to know that barbiturates were not the cause of the psychosis in the first place. The ordinary effective dose of 0.25–0.5 gm. might have to be increased by two or three times in a florid delirium.

Scopolamine, alone in 0.4–0.6 mg. doses, or combined with the barbiturates, has an infrequent indication. Small doses of benzedrine have been recommended to keep the patient awake during the day so that he may sleep at night.[84] The slow-acting barbiturates, the bromides and the opium derivatives have no place in the treatment of the toxic deliria.

Restraints are unhappy expedients to consider for use in an already fearful, apprehensive individual. Every improvisation should be tried to avoid their use. They are never necessary when good attendants are available to watch the patient. Properly applied restraint sheets may be required when tubs, sedatives and round-the-clock assistants are not accessible. The side rail is a device which should be used to prevent a patient from rolling out of bed. If he is strong enough to climb, side rails will simply increase the height of his fall.

Other Measures. If evidence exists that the cerebrospinal fluid pressure is increased, the use of mercurial diuretics, saline cathartics, salt-poor serum albumin, parenteral magnesium sulfate and spinal drainage might be rational. The sedative effect of magnesium sulfate makes this drug worth considering in the treatment of delirium. As a rule cerebral edema is not notably affected by these measures. Better results were obtained in the delirious reactions of the aged when 10 per cent glucose was substituted for 50 per cent glucose.[5]

It is understood that constipation and urinary retention will be corrected. Incontinence of urine during stuporous states predisposes to bed sores. An indwelling catheter and frequent turning of the patient will help prevent decubiti. Penicillin is frequently indicated as a prophylactic against hypostatic pneumonia.

Exhaustion, hyperthermia and shock are important causes of death in this condition. A state of functional adrenal-cortical insufficiency is not uncommon. Therefore, large amounts of aqueous or lipid adrenal cortical extracts or cortisone might effect a dramatic response. Intramuscular or intravenous ACTH has been recommended in the treatment of delirium tremens.[85,86]

SUMMARY

Like convulsions and coma, delirium represents a non-specific response to distortions of cerebral metabolism. The factors determining the onset of a delirious reaction are multiple; the most important are: the extent of exposure to the toxic agent, the premorbid personality structure, and the existing physical and psychic situation. The distinctive delirial pattern, with its delusional and hallucinatory content, is predominantly a reflection of the uncovered unconscious guilt, anxiety and depression.

Recognition of the toxic psychoses can be difficult, since organic and functional brain disorders and certain systemic diseases also participate in the delirial type of response. It is rare to encounter a toxic substance that produces a characteristic symptom complex, so that the differentiation of these agents often cannot be made on a clinical basis.

The management of this condition is fundamentally an effort to remove the offending toxin or to supply a missing metabolite. At the same time psychic and physiologic equilibrium must be restored. Neither the psychic nor somatic aspects of treatment should be ignored.

REFERENCES

1. Freeman, J. G. and Kolb, L. C. Acute intermittent porphyria. Associated psychiatric symptoms treated by electroshock. *Proc. Staff. Meet., Mayo Clin.*, 26: 401, 1951.
2. Strecker, E. A. and Lathbury, V. T. Tetraethylthiuram disulfide (Antabuse) therapy. *J. A. M. A.*, 148: 463, 1952.
3. Mortensen-Larsen, O. Psychotic phenomena provoked by tetraethylthiuram disulphide. *Quart. J. Stud. on Alcohol*, 12: 206, 1951.

4. Guild, J. and Epstein, N. B. Psychosis during treatment of alcoholism with tetraethylthiuram disulfide. *Quart. J. Stud. on Alcohol*, 12: 360, 1951.
5. Usdin, G. L. and Robinson, K. E. Psychosis occurring during antabuse administration. *Arch. Neurol. & Psychiat.*, 66: 38, 1951.
6. Fiske, D. Psychotic reaction to tetraethylthiuram disulfide therapy. *J. A. M. A.*, 150: 1099, 1952.
7. Curran, F. J. Current views on the neuropsychiatric effects of barbiturates and bromides. *J. Nerv. & Ment. Dis.*, 100: 142, 1944.
8. Isbell, H., Altschul, S., Kornetsky, C. H., Eisenman, A. J., Flanary, H. G. and Fraser, H. F. Chronic barbiturate intoxication. *Arch. Neurol. & Psychiat.*, 64: 1, 1950.
9. Morgan, N. C. Psychosis resulting from barbiturate withdrawal. *J. A. M. A.*, 149: 759, 1952.
10. Hewitt, R. T. A psychosis with barbiturate withdrawal. *J. Nerv. & Ment. Dis.*, 112: 526, 1950.
11. Heldt, T. J. Life Stress and Bodily Disease. Baltimore, 1949. Williams & Wilkins Co.
12. Jergers, H. and Brick, I. B. Hazard in the therapeutic use of morphine. *M. Clin. North America*, 34: 1761, 1950.
13. Levin, M. Partial or incomplete disorientation. *J. A. M. A.*, 129: 610, 1945.
14. Sensenbach, W. Bromide intoxication. *J. A. M. A.*, 125: 769, 1944.
15. Hodges, H. H. and Monroe, G. T. The continuing hazard of bromide intoxication. *Am. J. Med.*, 10: 459, 1951.
16. Tillim, S. J. Bromide intoxication. *Am. J. Psychiat.*, 109: 196, 1952.
17. Stetten, D. Recent contributions to the understanding of experimental diabetes. *J. A. M. A.*, 150: 971, 1952.
18. Jones, G. M. Posthypoglycemic encephalopathy. *Am. J. M. Sc.*, 213: 206, 1949.
19. Forster, T. L. Liver function and nutrition in relation to toxic psychoses. *J. Nerv. & Ment. Dis.*, 110: 1, 1949.
20. Brody, S. Psychiatric observations in patients treated with cortisone and ACTH. *Psychosom. Med.*, 14: 94, 1952.
21. Ransohoff, W., Brust, A. A., Reiser, M. F., Mirsky, I. R. and Ferris, E. B. The effect of sodium and potassium of the metabolic and physiologic responses to ACTH. Proc. Second Clin. ACTH Conf., p. 160. Philadelphia, 1950. Blakiston Co.
22. Rome, H. P. and Braceland, F. J. The psychological response to ACTH, cortisone, hydrocortisone and related steroid substances. *Am. J. Psychiat.*, 108: 641, 1952.
23. Clark, L. D., Bauer, W. and Cobb, S. Preliminary observations on mental disturbances occurring in patients under therapy with Cortisone and ACTH. *New England J. Med.*, 246: 205, 1952.
24. King, J. T. Digitalis delirium. *Ann. Int. Med.*, 33: 1360, 1950.
25. Grieber, M. F. Psychoses associated with the administration of Atabrine. *Am. J. Psychiat.*, 104: 306, 1947.
26. O'Flanagan, P. M. and Taylor, R. B. A case of recurrent psychosis associated with amphetamine addiction. *J. Ment. Sc.*, 96: 1033, 1950.
27. Norman, J. and Shea, J. T. Acute hallucinosis as a complication of benzedrine addiction. *New England J. Med.*, 233: 270, 1945.
28. McHag, J. F. and Scott, O. C. A. Acute psychosis caused by amphetamine. *Brit. M. J.*, 2: 1394, 1949.
29. Allentuck, S. and Bowman, K. M. Psychiatric aspects of marihuana intoxication. *Am. J. Psychiat.*, 99: 248, 1942.
30. Thale, T., Gabrio, B. W. and Salomon, K. Hallucinations and imagery induced by mescaline. *Am. J. Psychiat.*, 106: 686, 1950.
31. Rinkel, M., Deshon, H. J., Hyde, R. W. and Solomon, H. C. Experimental schizophrenia-like symptoms. *Am. J. Psychiat.*, 108: 572, 1952.
32. Hoch, P. H., Cattell, J. P. and Pennes, H. H. Effects of mescaline and lysergic acid. *Am. J. Psychiat.*, 108: 579, 1952.
33. Yapalater, A. R. and Rockwell, F. V. Toxic psychosis due to prophenpyridamine (trimeton). *J. A. M. A.*, 143: 328, 1950.
34. Waldman, S. and Pelner, L. Toxic psychosis due to overdosage with trimeton. *J. A. M. A.*, 143: 1334, 1950.
35. Sternberg, L. Unusual side reaction of hysteria from benadryl. *J. Allergy*, 18: 417, 1947.
36. Lott, G. N., Krug, E. S. and Glenn, H. R. A case report of drug delirium clinically interpreted as being due to pyribenzamine. *Journal Lancet*, 48: 242, 1948.
37. Bom, F. Delirium acutum after sulfonamide therapy of erysipelas. *Acta psychiat. et neurol.*, 21: 57, 1946.
38. Biskind, M. S. and Bieber, I. DDT poisoning: a new syndrome with neuropsychiatric manifestations. *Am. J. Psychotherapy*, 3: 261, 1949.
39. Kahan, V. L. Paranoid states occurring in lead petrol handlers. *J. Ment. Sc.*, 96: 1043, 1950.
40. Gutierrez-Noriega, C. and Von Hagen, V. W. The strange case of the coca leaf. *Scient. Monthly*, 70: 81, 1950.
41. Gorman, W. F. and Wortis, S. B. Psychosis due to thiocyanante treatment of hypertension. *J. Nerv. & Ment. Dis.*, 110: 46, 1949.
42. Barnett, H. J., Jackson, M. V. and Spaulding, W. B. Thiocyanate psychosis. *J. A. M. A.*, 147: 1554, 1951.
43. Steele, G. D. F. and Hegarty, H. B. Parieto-occipital syndrome following carbon monoxide poisoning. *J. Ment. Sc.*, 96: 1015, 1951.
44. Selikoff, I. J., Robitzek, E. H. and Ornstein, G. G. Treatment of pulmonary tuberculosis with hydrazine derivatives of isonicotinic acid. *J. A. M. A.*, 150: 973, 1952.
45. Roswit, B. and Pisetsky, J. E. Toxic psychosis following nitrogen mustard therapy. *J. Nerv. & Ment. Dis.*, 115: 356, 1952.
46. Asher, L. M. and Cohen, S. The effect of banthine on the central nervous system. *Gastroenterology*, 17: 178, 1951.
47. Welbourn, R. B. and Buxton, J. D. Acute atropine poisoning. *Lancet*, 2: 211, 1948.
48. Gorman, W. F. and Wortis, S. B. Psychosis in Addison's disease. *Dis. Nerv. System*, 8: 267, 1947.
49. Trethowan, W. H. and Cobb, S. Neuropsychiatric aspects of Cushing's syndrome. *Arch. Neurol. & Psychiat.*, 67: 283, 1952.

50. Cohen, S. Cushing's syndrome. *Ann. West. Med. & Surg.*, 4: 288, 1950.
51. Spillane, J. D. Nervous and mental disorders in Cushing's syndrome. *Brain*, 74: 72, 1951.
52. Selye, H. Adaptive reactions to stress. *Psychosom. Med.*, 12: 149, 1950.
53. Goldman, R., Reynolds, J. L., Cummings, H. R. and Bassett, S. H. Familial hypoparathyroidism. *J. A. M. A.*, 150: 1104, 1952.
54. Greene, J. A. and Swanson, L. W. Psychosis in hypoparathyroidism. *Ann. Int. Med.*, 14: 1233, 1941.
55. Fitz, T. E. and Hallman, B. L. Mental changes associated with hyperparathyroidism. *Ann. Int. Med.*, 89: 547, 1952.
56. Asher, R. Myxedematous madness. *Brit. M. J.*, 2: 555, 1950.
57. Brockman, D. D. and Whitman, R. M. Post-thyroidectomy psychoses. *J. Nerv. & Ment. Dis.*, 116: 341, 1952.
58. McGavack, T. H. The Thyroid. St. Louis, 1951. C. V. Mosby Co.
59. Drewry, P. H. and Wall, P. H. Mental reactions and their management in patients with cardiac disease. *Am. J. Psychiat.*, 94: 561, 1937.
60. Baker, A. B. and Knudson, J. Psychiatric aspects of uremia. *Am. J. Psychiat.*, 102: 683, 1946.
61. Liebowitz, S. and Gorman, W. F. Neuropsychiatric complications of viral hepatitis. *New England J. Med.*, 246: 932, 1952.
62. Fishberg, M. Postoperative psychosis. *Brooklyn Hosp. J.*, 6: 218, 1948.
63. Ficarra, B. J. and Lionella, J. Postoperative psychosis. *J. Internat. Coll. Surgeons*, 14: 111, 1950.
64. Cecil, R. L. and Loeb, R. F. Textbook of Medicine, 8th ed., p. 1540. Philadelphia, 1951. W. B. Saunders & Co.
65. Kline, C. L. and LaRue, S. H. Toxic psychoses with penicillin. *Ann. Int. Med.*, 28: 1057, 1948.
66. Brosin, H. W. Prognosis in some psychosomatic disorders. *Ann. Int. Med.*, 27: 745, 1952.
67. Levin, M. Toxic delirium precipitated by admission to the hospital. *J. Nerv. & Ment. Dis.*, 116: 210, 1952.
68. Doty, E. J. Incidence and treatment of delirious reactions in later life. *Geriatrics*, 1: 21, 1946.
69. Robinson, G. W. The toxic delirious reactions of old age. *Am. J. Psychiat.*, 99: 110, 1942.
70. Levin, M. Delirium. *Am. J. Psychiat.*, 107: 689, 1951.
71. Mackay, M. E., McLardy, T. and Harris, C. A case of periarteritis nodosa of the central nervous system. *J. Ment. Sc.*, 96: 470, 1950.
72. Rosenblum, M. J., Masland, R. L. and Harrell, G. T. Residual effects of rickettsial disease on the nervous system. *Arch. Int. Med.*, 90: 444, 1952.
73. Perk, D. Cerebral symptoms of thromboangiitis obliterans. *J. Ment. Sc.*, 93: 748, 1947.
74. Helfand, M., Houck, K. H. and Weissman, F. M. Trichinosis as a cause of encephalitis. *Dis. Nerv. System*, 13: 242, 1952.
75. Brain, W. R. Diseases of the Nervous System, 4th ed., p. 330. New York, 1951. Oxford Univ. Press.
76. Gendel, B. R., Young, J. M. and Kraus, A. P. Thrombotic thrombocytopenic purpura. *Am. J. Med.*, 13: 3, 1952.
77. Raymond, R. W. and Williams, R. L. Infectious mononucleosis with psychosis. *New England J. Med.*, 239: 542, 1948.
78. Winkleman, N. W. and Moore, M. T. Lymphogranulomatosis of the nervous system. *Arch. Neurol. & Psychiat.*, 43: 304, 1941.
79. Fantus, B. and Kraines, S. H. Therapy of acute delirium. *J. A. M. A.*, 115: 929, 1940.
80. Comroe, J. H., Bahnson, E. R. and Coates, E. O. Mental changes occurring in chronically anoxemic patients during oxygen therapy. *J. A. M. A.*, 143: 1044, 1950.
81. Beale, H. D., Schiller, I. W., Halperin, M. H., Franklin, W. and Lowell, F. C. Delirium and coma precipitated by oxygen in bronchial asthma. *New England J. Med.*, 244: 110, 1951.
82. Romano, J. and Engel, G. L. Delirium: electroencephalographic data. *Arch. Neurol. & Psychiat.*, 31: 356, 1944.
83. Margetts, E. L. Chloral delirium. *Psychiatric Quart.*, 24: 278, 1950.
84. Drewry, P. H. and Funkhauser, J. B. Management of delirium in a general hospital. *Virginia M. Monthly*, 77: 390, 1950.
85. Smith, J. J. Endocrine basis and hormonal therapy of alcoholism. *New York State J. Med.*, 50: 1704, 1950.
86. Fischbach, K., Simmons, E. M. and Randle, E. P. Delirium tremens treated with intravenously administered corticotropin. *J. A. M. A.*, 149: 927, 1952.

Seminars on Neuromuscular Physiology

The Myopathies: Including Their Appearance in Constitutional Disease*

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IT is the business of muscle to contract and the work which it performs, whether large or small in force or movement, is the primary gage of its state in health and disease. As simple as this task may appear to be, nevertheless, the diffuse distribution of muscle makes assessment of its functional status difficult to accomplish with much more precision than is employed daily by each physician who examines the general muscular strength of his patients. Despite the awful complexity of the many interwoven processes which effect muscular function,[42] the clinical manifestations of muscular disease are extraordinarily limited. It is entirely likely that manifold causes may lead to the same end results, and that in our present state of knowledge we are ignorant of most of them, yet the plain fact is that on clinical grounds we can recognize only three main symptoms of muscle dysfunction: (1) *Weakness* which may appear despite preservation of normal muscle bulk and consistency or which may develop concurrently with decrease in muscle size, *atrophy*. (2) *Limitation of motion* owing either to intrinsic changes in the muscle fiber as in "spasm," myotonic reactions or fibrosis, or as a result of restrictive changes in skin, joints, tendons, bones or fascia. (3) *Pain*, selected here as the overt symptom of inflammatory processes in general.

The small range of clinical manifestations with which muscle signals its disease has led naturally enough to attempts to sort out diseases on the basis of temporal evolution, genetic characteristics, anatomic distribution of involvement and response or lack of it to specific pharmacologic agents. When thorough understanding of cause is wanting, some classification of disease is made usually on the basis of gross and microscopic changes in structure. Concerning muscle, knowledge of structural change is extensive,[1] but the plain fact is that while most present day histologic technics may provide evidence that some disturbance has occurred, nevertheless, the pattern of reaction is one of discouraging stereotypy. In broad outline the kinds of changes to be seen are atrophy and pigmentation, hypertrophy, loss of striation, necrosis, degeneration of various forms, rearrangement and proliferation of sarcolemmal nuclei, invasion of inflammatory cells and phagocytosis, and fibrous replacement or regeneration. Unhappily, the same microscopic picture may be shared by diseases dissimilar in clinical aspect, and in some, little or no change has been discovered. It is hoped that in the future the newer technics of histochemistry, x-ray diffraction and electron microscopy, now being applied to a study of structure of normal muscle, may provide a higher degree of resolution of the changes underlying specific diseases of muscle.

It is our purpose here to describe a rough framework of uncertain boundaries into which may be placed patterns of muscular disease, some apparently arising from primary changes in the muscle cell, many others reflecting changes in muscle form and function which are the result of the interaction of this bulky and diffuse organ with other organs and tissues. For this purpose there have been excluded those diseases of muscle resulting from disorders of the central nervous system.[3]

It may be of interest first, however, to con-

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sider the role played by muscle in the general bodily economy simply by virtue of its bulk. Muscle constitutes some 40 to 45 per cent of body weight in normal adult man. The extent of participation by muscle in carbohydrate metabolism is suggested by the fact that the amount of glycogen stored in muscle is approximately equal to the amount deposited in the replete liver, although the mobility of liver glycogen is much greater and the glycogen as such in muscle is available only for local consumption. The intracellular mass of potassium in muscle accounts for some two-thirds of the total body content, of magnesium one-third, of phosphate one-tenth with the vast bulk of remaining phosphate sequestered in the skeleton. Some one-sixth of muscle is composed of specialized contractile proteins, a significant moiety of all the body proteins. These approximate distributions emphasize the probability that this mass of material, presumably requisite for normal muscle function, may suffer in the course of body-wide changes occurring in diseases which alter supply or synthesis of many primary units of metabolism.

TABLE 1
THE MYOPATHIES

Disease Limited to or Predominant in Muscle

"Primary" Myopathies:

1. Experimental induction: *tocopherol deficiency, methoxyquinoline*
2. Muscular dystrophies
3. Myotonias: *dystrophic, congenital or acquired*
4. Polymyositis
5. Periodic paralyses
6. Metabolic defects: *glycolytic (McArdle, von Gierke), myoglobin*
7. Miscellaneous: *amyoplasias, contractures, bizarre degenerations*

Muscular Reaction to Extramuscular Disease

Atrophy:

1. Denervation: *traumatic, neuropathic*
2. Disuse and fixation
3. Aging and cachexia

Endocrine:

1. Thyroid: *hyper, hypo*
2. Adrenal: *hyper, hypo*
3. Pancreas: *diabetes, hypoglycemia*
4. Pituitary: *acromegaly, Simmonds'*
5. Gonad: *virilism, castration*
6. Parathyroid: *hypo-, hypercalcemia*

Environmental:

1. Chemical: *ionic*
2. Vascular

Infection:

1. "Specific": *Trichinella, Toxoplasma, Coxsackie viruses*
2. General: *rickettsial, typhoid, pneumococcal pneumonia*
3. Post-infectious asthenia

Any attempt at sorting out the myopathies of necessity must be eclectic, establishing categories based on clinical pattern, on structural or functional alterations and, occasionally, on grounds which approach some understanding of cause. The classification proposed (Table 1) shares all of the weaknesses inherent in so mixed a bag. Nevertheless, it is presented with the aim of sketching out those diseases which appear to arise or be manifest predominantly in muscle and, in addition, to indicate the variety of other diseases which on occasion may produce significant dysfunction of muscle. With varying degrees of emphasis certain examples from this table will be examined below.

"PRIMARY" MYOPATHIES

"Primary" myopathy is a term which will be applied here not only to those entities which appear either to originate in muscle or to be confined to muscle, but also to those, not included in other categories, in which disturbance of muscle is the chief clinical feature of the disease. In this category fall (1) experimentally induced muscular dystrophies, (2) progressive muscular dystrophies, (3) the myotonias, (4) polymyositis, (5) some cases of family periodic paralysis, (6) other presumed metabolic disorders and (7) bizarre states not otherwise classifiable.

1. *Induced Muscular Dystrophies.* Disease of skeletal muscle has been produced in laboratory animals by dietary deficiency of vitamin C,[21] of vitamin E,[78] and by administration of cortisone.[33] The lesions resulting from vitamin E deficiency are particularly reminiscent of those occurring in human progressive muscular dystrophies and it was hoped that investigation of this nutritional muscular dystrophy would provide insight into the naturally occurring disease. Consequently a large body of information has accumulated pertinent to the role of vitamin E in the economy of skeletal muscle.

In the intact animal[95] and in his isolated skeletal muscle in vitamin E deficient dystrophy there is accelerated oxygen consumption. On the other hand, following administration of excessive amounts of vitamin E to normal animals there is depressed oxygen consumption in the intact animal[101] and in his isolated skeletal muscle, with impaired muscle carbohydrate metabolism.[103] Although study of experimental dystrophies has aided in understanding certain activities of muscle, it is unfortunate that most

of the evidence indicates that the dystrophy produced by vitamin E deficiency differs in important detail from progressive muscular dystrophy. Indeed, if a muscular dystrophy in man ever occurs as a consequence of vitamin E deficiency, the event must be rare.

For example, in dogs in whom an external biliary fistula has been created, vitamin E deficiency and consequent muscular dystrophy occur, presumably because tocopherols, being fat soluble, are unabsorbed from the gut.[11] On the other hand, examination of sections of skeletal muscle in infants who died of congenital biliary atresia, and who should, therefore, not have absorbed tocopherols, failed to reveal evidence of muscular dystrophy.[58] Again, in many cases of sprue the concentration of tocopherols in blood is low[23] but unequivocal evidence of muscular dystrophy is lacking. Dystrophies induced by means other than vitamin E deficiency have been less studied, but there is little reason to believe that any are identical with progressive muscular dystrophy.

The occasional extraordinary specificity of certain toxic substances for muscle is exemplified by the acute disintegration induced by plasmocid, a methoxyquinoline derivative.[47]

2. *Progressive Muscular Dystrophies.* These are almost always diseases of childhood although occasional instances spring up in middle life. Although the dystrophies were described more than a century ago, almost no progress has been made which permits coping with the diseases in a definitive sense. One pharmacologic agent after another has proved virtually useless. However, genuine economic and emotional gains derive from application of intelligent physical therapy. Frequently the dystrophy is complicated by atrophy of disuse, and it is this factor which is tractable; its management offers the patient the full available power of remaining intact musculature.

The dystrophies appear to be genetically determined. In the past, examination of pedigrees of dystrophic families led to a wide variety of genetic hypotheses.[6] The subject has been clarified by recent studies from the University of Utah.[91,92]

There are two main genetic types of dystrophy although other patterns of inheritance undoubtedly occur. Pseudohypertrophic muscular dystrophy is inherited as a sex-linked recessive with varying degrees of penetrance. In addition the mutation rate responsible for maintaining the disease appears to be quite high. Facio-scapulo-humeral muscular dystrophy is inherited as a dominant, also with a high mutation rate. It is important to recall that, despite the genetic differentiation, the clinical picture in an individual may include manifestations of both main forms. The familiar clinical course of these diseases need not be described here in detail. In general, pseudohypertrophic muscular dystrophy is characterized by onset during the first few years of life and by its relatively rapid course. Death occurs usually in the second decade from intercurrent infection, overwhelming weakness of the muscles of respiration or dystrophy of the myocardium. Facio-scapulo-humeral muscular dystrophy begins later in childhood and pursues a more leisurely course.

Occasional families are seen in which the pattern of the dystrophy is unique. In fact, it may not be amiss to suggest that each affected kindred has its own disease. A striking example is the family of some 500 members observed by Stanley Barnes.[5] Here the muscular dystrophy made its appearance when the patient was thirty to fifty years of age, but was preceded by apparent true hypertrophy of muscle. Peripheral muscles tended to be involved, never the sternal portion of the pectoralis major which is so characteristically affected in most dystrophies, and the course was unusually benign.

A diagnostic problem is presented by patients whose disease resembles progressive muscular dystrophy but in whose family no similar disease has been recognized. The disease often begins in the third or fourth decades of life, usually involves girdle muscle, may produce the typical lordotic posture, waddling gait and girdle wasting of progressive muscular dystrophy and tends to progress only very slowly.

Unfortunately microscopic examination of muscle need not supply a conclusive differentiation. Architectural differences between progressive muscular dystrophy and those diseases which it resembles are quantitative rather than qualitative. Perivascular infiltration by mononuclear cells appears occasionally in progressive muscular dystrophy, although it is more extensive in other states. Migration of sarcolemmal nuclei to the center of a muscle fiber commonly seen in progressive muscular dystrophy is observed, although rarely, even in muscle from normal individuals.

Some of these cases must be labeled progressive muscular dystrophy on the basis of the

appearance of the patient and a compatible histopathologic picture. In some instances these cases may represent true mutations. In others, however, despite the patient's unawareness of antecedent or collateral cases, examination of the family may reveal other cases, some overt and some so subtle that only absent deep tendon reflexes hint at the disease.

Many of these cases, however, are probably not progressive muscular dystrophy, but rather are a polymyositis.[1] Electromyographic evidence is beginning to appear suggesting that this differentiation may be made on physiologic grounds.[55,75] In 1936 Nevin[71] reviewed the reported cases of spontaneous progressive muscular dystrophy and described two additional cases. It is of interest that, in retrospect, McEachern[83] considered that Nevin's cases were examples of menopausal muscular dystrophy, a syndrome to be discussed later, while others today would prefer to call them examples of polymyositis.[24]

It is suspected that progressive muscular dystrophies are examples of "inborn errors of metabolism." The nature of the metabolic errors remains unknown and there is no reason to believe that a single or the same metabolic defect underlies all cases of progressive muscular dystrophy.

The disease is not limited to skeletal muscle. In many patients the myocardium shares in the dystrophic process. Whether or not smooth muscle, particularly in the intestines, is dystrophic is not clearly established.

For nearly half a century various endocrinopathies have been suspected[10] but no consistent pattern of endocrine dysfunction has been detected in patients with muscular dystrophy. Roentgenologic evidence of dystrophy of bone has been described in patients with muscular dystrophy, but the examples are not different from those seen in disuse atrophy of bone occurring during the growth period.

Efforts to elucidate the metabolic defects in patients with progressive muscular dystrophy have been handicapped by the difficulty in distinguishing cause from results of the disease. For example, creatinuria, long-considered the hallmark of muscular dystrophy, is a necessary consequence of loss of muscle mass in the presence of continuing synthesis of creatine,[102] and there is no evidence of disordered creatine metabolism in this disease. Ribosuria, recently reported to occur in progressive muscular dystrophy,[68] may prove to be relatively more specific, but it remains to be shown that it is not the result of disintegration of muscle fibers. Occasional instances of impaired carbohydrate tolerance have been reported. In some cases these have been the result of previous low carbohydrate diet; other cases may have represented loss of carbohydrate storage space consequent to loss of muscle mass. The basal metabolic rate, frequently low by normal surface area standards, is probably normal for remaining tissue, as can be shown by correcting the observed rate for loss of muscle mass.[81]

Analysis of the chemical composition of muscle is uninterpretable unless the results are adjusted to a reference base proportional to muscle fiber mass in the analytic specimen, as suggested by Hoagland.[49] A simple and useful reference base is the quantity of nitrogen, not incorporated in collagen or elastin; that is, essentially the nitrogen from muscle intrafibrillar protein.[61] When an acceptable reference base is employed, the composition of muscle in patients with progressive muscular dystrophy is found to differ from normal in certain respects: the potassium concentration of dystrophic muscle is low,[40] and the activity of certain glycolytic enzymes is reduced.[30] Along similar lines is the interesting observation that serum aldolase activity is increased in patients with progressive muscular dystrophy.[84] For the time being these observations serve as clues for further study; they are not yet interpretable in terms of a prime cause of dystrophy.

3. *The Myotonias.* Myotonia is a physical sign characterized by apparent inability to relax a stimulated muscle. The phenomenon has been produced experimentally,[35] has been studied in a kindred of goats in whom it appears as an hereditary disease[12] and has been investigated in man.[25,26,57] Analysis by electrophysiologic technics has showed the basic change to be a repetitive response of the muscle fiber to a single stimulus or a short volley. Although it would seem certain in the goat and likely in man that this repetitive response arises only in the muscle, the clinical feature of after spasm has suggested that perhaps proprioceptive sensory organs affected by the myotonic muscle alter reflex patterns occurring more centrally.

The myotonic phenomenon is obliterable by repeated stimulation, either voluntary, electrical or mechanical. Whatever the cause, it is intrinsic in muscle and not in the myoneural

junction or in nerve. It can be erased by quinine but not by curare.

Myotonia appears occasionally in association with or following some systemic diseases. It is seen infrequently in myxedema[56,76] and disappears when the myxedema is corrected. It occurs during or following peripheral neuritis, usually infectious neuronitis, and disappears eventually, although it may persist for several years.[53] Even less commonly it has been observed following a number of apparently unrelated infections or traumatic states. These temporary myotonias, known as myotonia acquisita, are obliterable by quinine, but they are seldom really troublesome and most patients prefer the mild myotonia to cinchonism.

Myotonia appears as a primary phenomenon in two hereditary diseases, myotonia congenita and myotonic dystrophy. Despite evidence that the microscopic picture of muscle in myotonia congenita resembles that of early forms of myotonia dystrophy[98] and that the two diseases have occurred in the same family,[64] it is generally held that these are separate entities. Certainly the generalized myotonia of the congenital form stands in contrast to the usual localization in hands and tongue seen in the dystrophic variety.

In myotonia congenita, apart from myotonia, the patient appears quite normal or may even exhibit superb muscular development. The myotonia is apt to be an annoyance, and some but by no means all of these subjects are relieved by quinine or by quinidine.

In myotonic dystrophy, on the other hand, myotonia is but one manifestation of widespread disease.[17,96] This disease usually makes itself known in the third and fourth decades or later, although certain stigmata may have been present for years. Of the dystrophies seen in this age group, myotonic dystrophy is probably more common than progressive muscular dystrophy.

The presenting complaint is apt to concern difficulty in walking; patients often note that their legs drag as though they were walking waist-deep in water. Nevertheless, the most striking muscle involvement, at least early in the disease, is about the head and neck. The temporals and masseters are wasted, the orbicularis oris is weak, atrophy of the muscles of expression irons out the face. Virtually pathognomonic, however, is involvement of the sternomastoid, which begins to atrophy early and soon becomes a mere fibrous strand, so that the patient walks with his head fallen forward, and when he lies down he can scarcely, if at all, raise his head off the pillow. Usually slowly, the dystrophy progresses to nearly all muscle groups, so that the outcome resembles that of progressive muscular dystrophy. Myotonia may be inconstant and may not be demonstrable particularly in grossly wasted muscles.

It is quite certain that this disease is not limited to muscle. Patients and members of their family tend to develop cataracts. There is often a high arched palate and frequent association with hyperostosis frontalis has been noted. Both men and women have early frontal baldness which may precede overt muscle disease by more than a decade. Males nearly always have loss of potentia, reduced urinary excretion of 17-ketosteroids,[7] increased urinary excretion of follicle-stimulating hormone, loss of spermatogenesis and, occasionally, gynecomastia. Women are perhaps less apt to show evidence of gonadal insufficiency. In both sexes gonadal disturbance is a late manifestation of the disease, probably occurring after well established dystrophy. The occurrence of other endocrinopathy is inconstant and usually only suggestive.

Although the muscular damage may be as extensive as in patients with progressive muscular dystrophy, patients with myotonic dystrophy excrete amounts of creatine which are trivial compared to that expected in the presence of such marked loss of muscle mass.[67] On the basis of this and collateral observations it has been suggested that synthesis of creatine may be retarded in this disease.[102] This is not an explanation of the disease, but it may be another manifestation of widespread disturbance in handling nitrogenous substrates which may underlie the disorder.

The dystrophy has resisted treatment. Androgens, adrenal cortical steroids, thyroid substance and many vitamins have not proved convincingly useful. As in progressive muscular dystrophy, some help may be anticipated from attention to the psyche and from intelligent physical therapy. The myotonia is often inconsequential to the patient and may not require management.

4. *Polymyositis and Dermatomyositis.* This group of diseases is defined by microscopic evidence of widespread inflammatory processes in skeletal muscle with which no specific causative agent is associated. It is probably the commonest

primary myopathy of adult life and it is likely that a number of patients, who have developed in middle life a disease thought to be progressive muscular dystrophy, have suffered in reality from polymyositis.

The clinical spectrum of the polymyositides is broad.[72] Onset may be insidious or explosive, with or without fever or muscle pain or tenderness. Eruptions, if present, are non-specific. Affection of joints may occur and resembles that of rheumatoid arthritis. In some cases there may be palpable nodules in muscle, usually poorly circumscribed. Often the skin feels thickened and the examiner has the impression that it cannot be picked up free from underlying muscle. These diseases mimic cachectic states, rheumatoid arthritis, lupus erythematosus disseminatus, polyarteritis nodosa, scleroderma, thyroid myopathy, Addison's disease and progressive muscular dystrophy. Although diagnosis rests on microscopic examination of muscle so that biopsy of skeletal muscle should be performed in adults with obscure muscle wasting, nevertheless, as has been indicated, histologic features of polymyositis are only quantitatively different from those of some of the diseases with which it may be confused.

The closeness with which polymyositis mimics other states may be illustrated by the following examples:

M. S. (J. H. H. No. 585427), a nineteen year old housewife, began to have difficulty climbing stairs ten months prior to admission. A few weeks later she noticed easy fatigability of her arms so that she had difficulty in lifting. Weakness increased progressively until she could not climb stairs at all and could elevate her arms beyond the horizontal position only briefly. At no time during her illness did she have feverishness, pain or muscle tenderness. No one in her family was known to have muscle disease.

Her appearance suggested to all observers that she had progressive muscular dystrophy. Her scapulae were winged; she was unable to rise from a kneeling or squatting position. Weakness was greatest in the muscles of the shoulder and pelvic girdles, particularly the deltoids, latissimus dorsi, rhomboids, tensor fasciae latae, gluteus maximus, and flexors and external rotators of the hip although few muscles had normal strength.

Biopsy of the deltoid revealed atrophy of striated muscle with scattered foci of leucocytes, mostly lymphocytes, but occasionally large mononuclear cells and polymorphonuclear leukocytes. There was very little proliferation of sarcolemmal nuclei. On the basis of this evidence of subacute necrosis of muscle a diagnosis of polymyositis was made.

E. R. (J. H. H. No. 597635), a fifty-seven year old widow, entered the hospital because of generalized wasting and weakness. She was well until two years prior to admission when she began to lose vigor and noticed numbness of her fingers, particularly in the cold. The main course of her illness perhaps began a year later when she complained of greatly increased fatigability, especially of the muscles of her back and lower extremities. At the same time there appeared increasing brownish pigmentation over the hands, wrists, sternum and subclavian region. The skin over these areas and over the medial surface of the arms became dry, brittle and scaly. With this she became aware of increasing emotional tension and instability. About six months later the progress of her disease accelerated. Her appetite began to flag and weight loss became marked so that ultimately she lost 40 pounds or one-third of her body weight. She complained of blurred and double vision. Her voice became so faint her family could not understand her. Fluid regurgitated through her nose and solid food was swallowed with difficulty. She sought medical advice in another clinic where it was found that her weakness was not ameliorated by neostigmine and that the thyroidal uptake of a tracer dose of I^{131} was accelerated. Accordingly, she received a therapeutic dose of I^{131} to which she seemed to have a slight transient response. Nevertheless her condition deteriorated and ten weeks after the dose of I^{131} she was admitted for further study.

She was markedly enfeebled and appeared much older than her stated age. She had obviously lost a great deal of weight. Her speech was slow, her voice indistinct and frequently nasal. There was exophthalmos and divergent strabismus. Axillary hair was almost absent. Over bony prominences the skin was thin, glazed, dry and cracked. Elsewhere the skin was freely movable and elastic. Over the sternum, forearms and hands there was bronzing.

No muscle tested was normal. The left side of her face sagged. Neck muscles were almost functionless. Proximal muscles, in general, were weaker and more wasted than distal. Deep tendon reflexes were markedly diminished.

Her blood pressure varied from 86/60 to

105/75 mm. Hg and she had persistent tachycardia, to 120 per minute.

The possibilities considered were thyroid myopathy, myasthenia gravis, Addison's disease, a progressive polyneuritis, porphyria and dermatomyositis.

Following administration of 20 mg. of ACTH the eosinophils disappeared from her peripheral blood. Nevertheless, during her stay in the hospital the concentration of sodium in serum fell from 134 to 124 mEq. per L. and of chloride from 93 to 76. She did not have porphyria.

Her basal metabolic rate was +27 per cent of normal. Concentration of serum cholesterol was 298 to 355 mg. per 100 ml. The rate of uptake as well as the total accumulation of radioiodine by the thyroid gland were in the high-normal range, consistent with slightly increased activity of the thyroid.

Biopsy of pectoral muscle showed scattered atrophy with perivascular collections of lymphocytes, in some areas quite numerous.

In the face of indecisive evidence a course of *n*-propyl thiouracil was instituted in the hope that she had hyperthyroidism. Although she felt better briefly, her deteriorating course continued, in the main. She did not return for reevaluation, but some seven months later entered the Mayo Clinic under the care of Dr. Robert M. Salassa, to whom we are indebted for further information. She was quite emaciated and enfeebled and died after a few days. Dr. Salassa's opinion that the disease was dermatomyositis was confirmed at autopsy.

Menopausal muscular dystrophy was the name given a disease exhibited by a group of patients, one a man, in whom weakness and wasting of girdle muscles appeared late in life.[77] Histologically, there was necrosis of muscle with scattered foci of mononuclear cells, a picture which suggested vitamin E deficiency to some, but polymyositis to others.[24] The disease was reported to respond clinically to administration of vitamin E or of cortisone,[83] but these reports have not yet been confirmed by microscopic re-examination of muscle.

The polymyositides are therapeutic problems in which assessment of therapy is treacherous. In a large fraction there is spontaneous remission either permanent or for extended periods. It has not been possible to predict the natural course of the disease although, in general, the more rapid the initial progress of the disease, the worse the immediate prognosis.

No therapeutic agent has been uniformly useful. Although the role of corticotropin or of cortisone is evaluated incompletely, in a small minority of cases the effect of these agents is sufficiently dramatic to merit their use in conjunction with supportive measures. Those cases which appear to have responded have lacked obvious features which might serve as criteria for selection.

5. *Some Cases of Family Periodic Paralysis.* Family periodic paralysis describes a group of diseases characterized by transient episodes of paralysis, beginning usually in the lower extremities and ascending, appearing in several members of a kindred.[88] In some individuals, and typically in some kindreds, the disease becomes associated after a time with atrophy of muscle.[8] Occasionally, pseudohypertrophy of the calves has been described. Microscopic examination of muscle has failed to reveal a consistent pattern, but there have been reports of large numbers of intrafibrillar vacuoles in atrophic muscle which, in the case of one family, contained material reacting as glycogen.[93] It is of interest that in this family no alteration of serum potassium concentration occurred and the paralysis did not respond to administration of potassium salts.

In the light of observations such as these, family periodic paralysis may be considered but a symptom common to a number of yet unknown underlying defects.

6. *Other Presumed Intrinsic Metabolic Disorders.* Although it is suspected that some of the states previously discussed represent intrinsic failure of normal metabolic processes in skeletal muscle, there are a few states in which it is more apparent that the disease is actually one of altered metabolism. These include McArdle's syndrome, myoglobinuria and von Gierke's disease, the last of which will not be considered further here.

McArdle's syndrome: McArdle[65] described a seemingly normally muscled young man whose muscles went into painful spasm with moderate effort and in whom muscular work was, therefore, limited. McArdle's studies led him to conclude that the muscles of this patient were defective in one of the intermediate enzymes concerned with muscle glycogen breakdown; and he speculated that in a multi-enzyme system as complex as that concerned with carbohydrate metabolism in muscle it would not be surprising to discover an occasional, presumably

inborn, error. One of the intriguing possibilities arising from McArdle's discovery is that such an error of metabolism might be concerned in the easy fatigability of some persons whose obscure complaints have hitherto been dismissed as of emotional origin.

Myoglobinuria:[14,54] Myoglobin is an iron-containing pigment, a pyrrole bound to a protein, about one-fourth the molecular weight of hemoglobin, abundant in muscle and with great affinity for oxygen. When muscle is damaged, myoglobin may spill into extracellular fluid and thence into plasma. Since it is a relatively small molecule, it is easily and presumably completely filtered by the renal glomeruli. In man the renal threshold for myoglobin, unlike that for hemoglobin, is minute, if it exists at all, and virtually all filtered myoglobin appears in the urine to which it imparts a deep color, brown, burgundy, to black. The urinary myoglobin can be distinguished spectroscopically from hemoglobin. Under certain conditions the explanation for which is disputed, myoglobinuria is associated with renal damage as in hemoglobinuria, and renal insufficiency may be the urgent clinical problem.

Myoglobinuria is produced by crushing injury, by ingestion of an unidentified toxic substance (Haff disease), and it occurs spontaneously.

Spontaneous myoglobinuria is an episodic disease although death may occur in a first attack. It has appeared at all ages. In some instances the attacks may follow muscular exercise; they can sometimes be reproduced by exertion specific for the patient. Onset is sudden, sometimes with fever, nausea and vomiting. Involved muscles, whether few or general, are painful, spastic and weak, and sometimes swollen. It is then that pigment appears in the urine. The patient may recover in a few hours although sore muscles may remain for days, or acute and fatal renal insufficiency may supervene.

There is more to the disease than simple seepage of myoglobin from muscle. Examination of muscle reveals widespread architectural damage, and other muscle constituents, notably creatine, accumulate in blood and urine during the attacks. Persistent atrophy of muscle has been described.

The disease resembles acute porphyria, but myoglobin, detected by the benzidine test, does not react to Watson's test for urinary porphobilinogen. Myoglobinuria can be suspected by the finding of pigmented urine, giving a positive benzidine test without red blood cells in the urine, in the absence of evidence of hemolysis. Since myoglobin is so rapidly excreted in the urine it does not accumulate in plasma and the plasma will not have the red tint of hemolysis.

7. *Miscellaneous and Bizarre Degenerations.* In a tentative classification, not yet based on sound physiologic principles, there must be room for those even more mystifying diseases which do not fit into any named category. There are patients with weakness, wasting and strange necrosis of skeletal muscle in whom no satisfactory diagnosis has been made. It is possible that, in some of these, technics such as those used by McArdle may illuminate the problem.

ATROPHY

One of the challenging problems which baffles further understanding of certain reactions of muscle to extramuscular influences concerns the several processes included in the term atrophy. It is accepted, without necessarily understanding the cause, that certain tissues and organs hypertrophy under an increased work load and lose bulk when the load is diminished. In addition to skeletal muscle itself, familiar examples spring to mind in bone, lymphoid tissue, myocardium, kidneys and adrenal cortex. While the stimuli, or lack of them, and their effect on the tissue or organ are clear, and while from a teleologic viewpoint the responses are appropriate, nevertheless it needs re-emphasis that the chain of events is very obscure indeed. In the case of skeletal muscle the fact that atrophy follows disuse and fixation of joints is well appreciated; perhaps somewhat less well remembered is the rapidity with which such reduction in muscle mass and power may ensue, and the minimal amount of activity necessary to forestall or slow the development.[31,32] Without gainsaying the necessity for rest in bed as a therapeutic measure in a number of circumstances, it can be said fairly that muscle atrophy, both general and specific (e.g., quadriceps), occurs in patients confined to bed with more frequency and severity than is reasonable, because the simplest sorts of brief and almost effortless exercises suffice to minimize or prevent these changes. It cannot be said that the prolonged muscle weakness which follows inactivity or episodes of infection, as for example after pneumococcal or atypical pneumonia or hepatitis, is purely muscular in origin; but it is

clear that in some of these cases the loss of muscle bulk would appear to contribute importantly to the disability that develops. Awareness of the explosive rate of atrophy from disuse will suggest simple means of preventing it. In other circumstances in which alterations in joints and supporting tissues limit muscular activity, the maintenance of muscle bulk may become much more difficult to insure. However, an understanding of the inevitable development of this process may sometimes provide an explanation for bizarre or peripheral symptoms which are not accounted for by the primary disease.

Both aging and cachetic inanition are notorious in their capacity to reduce muscle mass. Again, no clear causal explanation of their development is at hand, but the severity of atrophy seen may be of such degree that the differentiation from more specific myopathies may be extremely difficult. Conversely, of course, extreme examples of senescent atrophy may be thought to represent a manifestation of some less general process.

Aside from the kinds of atrophy indicated there is a special form which follows interruption of functional continuity from neurone, across the neuromuscular junction, to the muscle fiber itself: the atrophy of denervation. In its most striking form it follows severance of a motor nerve or central destruction of the motor neurone, but commoner, perhaps, are the partial denervations which follow neuropathy produced by a host of differing diseases. Examples are provided by metabolic (diabetes), vascular (arteriosclerosis), nutritional (B_{12} deficiency), infectious (polyneuronitis) and toxic (heavy metals) processes.

The underlying physiologic problem of what occurs in muscle isolated from its nerve is more complex than that in muscle atrophied by disuse, although neither mechanism is understood. The features which distinguish denervated muscle are the appearance, within a few days, of spontaneous activity in the form of fibrillation[27] and exquisite sensitivity to a variety of neurohumoral agents.[16] That this might represent a reversion to a more primitive stage has been suggested on the basis of the observation that embryonic muscle fibers display a form of fibrillation prior to innervation as do muscle fibers growing in tissue culture.[59] With respect to chemical constitution of denervated muscle[39,48,79] there are a few clues compatible with but by no means establishing the concept of a reversion toward an earlier state: glycogen stores diminish and the concentration of certain enzymes involved in carbohydrate metabolism drop toward embryonic levels.[69] Of especial interest in this connection is the recent preliminary report by Rowe[78] that a Coxsackie virus, hitherto found incapable of multiplication in muscle of adult mice, in contrast to its growth in muscles of suckling mice, multiplied vigorously in adult mouse muscle denervated two weeks before inoculation. Here is another bit of evidence that profound alterations in the constitution of the muscle follow on its separation from its neural supply.

ENVIRONMENT

Muscle, in common with all cells, operates efficiently only when the physicochemical anatomy of its contents and its surrounding interstitial bog is maintained within an extraordinarily limited range of variation.[85] The list is long of disturbances which may so distort these inner and outer environments that the muscle cell no longer performs its task in full strength or capacity. More to wonder at, perhaps, is the ability of stabilizing mechanisms to guard the composition of these milieux against the dislocations produced by failure of regulatory systems and by excesses and deficiencies of required substances induced by abnormalities in supply. The state of the analytic art has focussed attention on the ionic constituents and water distribution of cells and their immediate environment in relation to their function;[74] earlier, the methods of balance studies available had made assessment of total exchange accessible; more recently estimates of internal transfers have been made for certain important ions.[22] The description of changes in intracellular composition in man is still primitive, largely because of the great difficulties encountered in analysis and the lesser availability of tissue for study.[4] Nevertheless, there may be seen certain patterns of reaction which accompany specific disturbances in ionic composition. It would, however, be shortsighted to lose awareness of the virtual certainty that what we observe clinically as the final product of disease almost surely results not only from changes in ionic and watery composition but also from alterations in protein and carbohydrate substances and enzymes which may be sequels to or separate from the elementary changes which we measure.[15]

Two fundamental processes of muscle function are excitability and contractility.[86] How excitation evokes contraction is quite mysterious but the participation in these functions by certain ions is becoming clearer. The sign of excitability, a change in electrical potential, is dependent on a chemical potential created by large differences in ionic concentrations established between the inner and outer phases.[50,63] During the explosion of activity sodium rushes into the cell, followed immediately by an outward leak of potassium. Changes in chemical potential resulting from alterations in concentration of Na and K in the immediate environment of the muscle fiber have been shown to produce effects on the electrical potential concerned in excitation. The behavior of the intracellular contractile proteins, perhaps the ultimate unit which effects shortening of the fiber against resistance, likewise is conditioned by the concentration of several cations.[87] When it is considered at how many loci in a complicated chain of events the proper control of ioniccon centration becomes essential for function, there can be little less than astonishment that anything works at all.

Almost all that is known about the effects wrought on muscle function by chemical changes has been obtained by experiments requiring extraordinary isolation of tissues and organs. In the intact animal or in man the interaction of compensating systems makes analysis treacherous. When disease supervenes the complexity is compounded,[46] and the equating of a response to one or another measured change is apt to lead only to a partial understanding. Nonetheless, clinical patterns do appear which are associated with recognizable chemical disturbances; what requires emphasis is the probability that the present day capacity to detect the entire chemical lesion is limited and only fragmentary in extent. Because of the close functional relationship of muscle to nerve and because both tissues employ many identical or analogous operations, it frequently becomes impossible to unravel the effects of chemical disturbances on muscle from those playing on the neuromuscular unit as a whole. Conversely, effects attributed mainly to disordered function in nervous tissues may have an important but obscure counterpart in muscle. Emphasis has been put on these confusing features to make clear that there runs through what is to follow the constant implication that causal relations are not likely to be as simple as they may appear.

The muscular weakness which follows depletion of sodium in man has been described especially vividly by McCance[66] who observed the results of experimental acute and drastic salt depletion. The outstanding development in respect to muscle was weakness. The added development of cramps, especially in calf, forearm and abdominal muscles, which is seen in some circumstances during the performance of heavy work in a hot environment[28,29] (miners' or heat cramps) has been attributed usually to acute loss of salt in sweat, largely because the repletion of salt alleviates the cramps. Whether this is the whole story is not so clearly established. The forcible replacement of intracellular K by Na under the influence of desoxycorticosterone leads to remarkable muscular weakness in dogs,[37] and the similar event seen in man is likely to be the result in part of the same disturbance in chemical constitution. As will be described, the muscular weakness characterizing hypoadrenalism is less clearly attributable to distortion of ionic patterns alone.

In the case of potassium the last decade has seen a remarkable spate of clinical observations relating disturbances in the concentration of potassium in serum to muscular weakness. The earlier examples recognized in instances of chronic nephritis,[13] renal insufficiency[38] and vigorous treatment of diabetic acidosis[51] have been expanded by the discovery of similar occurrences in almost every circumstance in which loss or retention of potassium might be anticipated. It requires the most strenuous emphasis that muscular weakness does not inevitably follow lowered concentrations of potassium in serum. In fact, over-all the coincidence may well be less frequent than a lack of it.[90] Although no new understanding of the causal relation between potassium and periodic paralysis has developed,[88] the converse situation is represented in this assortment of disorders in which there are undoubted examples of paralysis without accompanying changes in the level of potassium in the serum.[93,97]

The modulating functions of calcium and magnesium in the regulation of excitation and contraction are known to be critical. Lowered concentrations in the cellular environment of both these cations lead to irritability and accumulations of them depress.[34] Tetany, which is a neural manifestation, may well have a counterpart clinically in muscle activity when seen in conjunction with hypocalcemia or

hypomagnesemia. During extreme accumulations of calcium in serum striking muscular weakness develops; the paralyzing effect of magnesium accumulations is well known from animal and human experiments, but its recognition in the course of disease is not certain because it occurs usually in association with other sweeping disturbances. Magnesium, which constitutes so large a portion of intramuscular cation, has been studied but little in disease and its significance is understood virtually not at all.[4]

The part played by anionic constituents is obscure, largely because when alterations in bicarbonate, chloride and phosphate concentrations are encountered simultaneous changes in cationic distributions have occurred. Thus it is unlikely that changes in muscle function may be attributed solely to any single anionic disturbance nor to alterations in hydrogen ion concentrations in body fluids. Certain it is that in the face of such alterations, and others concurrently, disordered muscle function is observed. With respect to intracellular distributions in disease even less is known. The large intramuscular store of phosphate as well as the smaller supply of sulfate must enter into the maintenance of muscle function,[62] but how they are involved in general and local disease is unknown.

It might be thought that this array of uncertain relationships between chemical disturbances and the function of muscle could be taken to mean that such interplay does not exist. It seems more likely that more such relationships exist than we may even suspect, but that in many circumstances the reactions are more complex than our present day methods of analysis are capable of resolving.

ENDOCRINOPATHY

Since a major role in regulating blood supply, composition of the internal environment and intracellular metabolism is played by the endocrine system, and since excitable tissue depends on a nice regulation of these factors, it is to be anticipated that skeletal muscle, the largest end-organ in the body, suffers in the face of over- or underactivity of various endocrine glands. That certain hormones may have a more specific effect on the performance of contractile elements of the muscle fiber itself is suggested strongly by the recent observations of Csapo and Corner on a special end-organ, the myometrium.[19,20] The response of skeletal muscle to experimental deprivation or plethora of specific hormones has been widely studied and described, but in naturally occurring disease the more dramatic responses of other organs and tissues to endocrinopathy is apt to obscure disorder of skeletal muscle. However, in certain states, signs and symptoms referable to skeletal muscle are so prominent as to cause confusion with primary myopathies.

Thyroid. Muscle disease of varying extent is almost always present in *hyperthyroidism;* quadriceps weakness is particularly easy to demonstrate even in the absence of gross atrophy. In typical exophthalmic goiter with hyperthyroidism there is loss of weight owing in considerable part to loss of muscle mass. In consequence of dissolution of muscle there is an accumulation of creatine in plasma in excess of the renal threshold for creatine, and creatinuria occurs.

Whether muscle disease in hyperthyroidism is consequent upon excesses of thyrotropic hormone or of thyroid hormone or of both is unsettled. Lesions of skeletal muscle have been produced experimentally both by administration of thyroxine, with hyperthyroidism, and by administration to thyroidectomized guinea pigs of thyrotropic hormone.[29]

Although muscle wasting is usual in hyperthyroidism, when it is the most striking clinical feature of the disease, the entity has been called *chronic thyrotoxic myopathy.*[9] Such patients often lack the obvious classical signs of hyperthyroidism and in them the cause of muscle wasting may be obscure. The disease resembles the cachexia of carcinoma, polymyositis, Addison's disease and progressive muscular atrophy, with which it has been confused; although if hyperthyroidism is suspected, the diagnosis is easily established by the usual means.

The possibility exists that in at least some patients with chronic thyrotoxic myopathy the disease differs fundamentally from classical hyperthyroidism. Although more women than men have hyperthyroidism, the sex incidence is reversed in thyrotoxic myopathy. These patients are apt to be beyond fifty years of age, they tend not to have goiter, exophthalmos, more than slight tachycardia or spectacular hyperkinesia. Despite the loss of, on the average, a quarter of their body weight (perhaps half their muscle mass as suggested by the daily urinary excretion of creatinine), they have relatively trivial or no

spontaneous creatinuria in contrast to the marked creatinuria of exophthalmic goiter.[100]

Although no adequate explanation of these differences is available, the disease responds to antithyroid therapy. With administration of goitrogenic agents strength is regained and body weight is restored in about six months although the time for complete restoration varies greatly. Among the diseases with which it is confused, chronic thyrotoxic myopathy is the most benign illness the patient might have in the sense that response to therapy is total and reliable. However, deaths have been reported in untreated patients, in all cases probably due to extensive atrophic impoverishment of the muscles of respiration.

Less common in hyperthyroidism is a flaccid paralysis, resembling periodic paralysis, associated with marked hypokalemia and amenable to replacement of potassium. In a small per cent of patients with hyperthyroidism, but more commonly than in the population at large, there is concomitant myasthenia gravis. In such cases, in addition to the weakness of myasthenia gravis, the intrinsic muscular atrophy of hyperthyroidism may be superimposed. Although this coexistence is an enigma, management of the hyperthyroid element presents no unique problem.

Several affections of muscle have been observed with *myxedema*.[56] A low basal metabolic rate is common in progressive muscular dystrophy and in myotonic dystrophy but there is no evidence that hypothyroidism is concerned with these diseases. However, an occasional patient with hypothyroidism may exhibit myotonia. More often patients with myxedema are simply slow in relaxing muscle, but do not exhibit mechanical myotonia or the electromyographic manifestations of myotonia. In some of these patients there is true hypertrophy of muscle associated with weakness. All the abnormal muscular phenomena have disappeared *pari passu* with subsidence of the myxedema.

Adrenals. Weakness is a familiar manifestation of adrenal insufficiency. Observation of adrenalectomized animals has suggested that since, during muscular exercise, blood pressure fell before work performance became impaired, weakness of Addison's disease may be chiefly secondary to circulatory inadequacy.[44] Nevertheless such severe distortion of ionic composition of skeletal muscle accompanies adrenalectomy[70] that it is unlikely that muscle metabolism can proceed at a normal pace. Localization of those metabolic defects which produce weakness remains speculative at present, but it has been observed that cortisone, *in vitro*, hastens the polymerization of actin, a contactile protein of muscle.[18]

There is considerable overlap between the clinical pictures of Addison's disease, of chronic thyrotoxic myopathy and of polymyositis, and, indeed, the suspicion persists that elements of adrenal insufficiency may be present in the two latter states although evidence for it is inconstant.

Parathyroid. Weakness, pain and atrophy of skeletal muscle have been reported as major complaints in hyperparathyroidism, masking the fundamental disorder.[94] Since the role of parathyroid hormone in muscle metabolism is not established, the mechanism of this disturbance is unexplained.

Pancreas. Easy fatigability and muscle wasting are, of course, common in unregulated diabetes mellitus, but the total picture is not apt to resemble primary myopathy in the absence of neuritis. Diabetic neuritis, as is true of any peripheral neuritis, may be difficult to distinguish from primary neuromuscular disorders, and in an occasional patient atrophy and weakness of distal muscles may be the chief manifestation of the disease. The not infrequent occurrence of nocturnal muscular cramps in the unregulated phase of diabetes would appear to be a different phenomenon. Its explanation is not clear but there is some suggestion from experimental investigation in the rat that hyperglycemia *per se* may lead to intense irritability of the muscle fiber.[60] It is curious that although skeletal muscle has been a favorite test tissue for study of carbohydrate metabolism no proven explanation exists for the weakness so common in long-standing, mild diabetes.

INFECTIONS

The impact of infectious disease on muscle may be viewed as occurring in two different major forms. In one the infecting agent enters the muscle itself. Within this category at one end may be placed the nematodal infestation with Trichinella in which the primary site is skeletal muscle itself, although myocardium and nervous system invasion may be of serious and overshadowing importance.[45] In other diseases of protean manifestation, such as tuberculosis and

spirochetal diseases, there may be less frequent invasion of host muscle by the organism.[82] Then there are diseases which ordinarily are not considered to involve the musculature but which on occasion make themselves manifest clinically with an overwhelming attack on muscle so that the origin of the disease is suspected of being essentially muscular. An example of this form of infection may be seen in the recent reports of toxoplasmosis occurring in adults in whom careful search has revealed invasion of muscle in some instances, consonant with certain of the symptoms which had developed.[2,80,86] The recent definition of a group of interrelated viruses, the Coxsackie viruses, has brought to the fore the possibility that virus multiplication in skeletal muscle might underlie certain poorly understood myositides.[43,52] These then are examples of muscle disease which develop when the muscle itself is invaded by a parasitic agent.

In addition there are seen widespread acute degenerative changes in muscle which accompany serious infectious diseases in which there is no evidence that the offending organism ever gains lasting entry into the muscle. Representative of those in which the cause of extensive damage to muscle is plain is typhus and related rickettsial disease. In this instance the damage to the intimate vascular supply would appear adequate to explain the associated destruction of muscle. Less understandable are those degenerations, classified as the Zenker hyaline type, which follow typhoid fever,[99] pneumococcal pneumonia[41] and other serious and acute infections. Rank speculation might suggest that these lesions result from the action of exotoxins, reminiscent of certain chemical agents which damage muscle, more or less selectively, but evidence for any hypothesis is lacking.

The generalized muscular weakness which follows infection has been referred to before. Its clinical features are a matter of personal experience for almost everyone, and are made especially impressive by the unreasonably protracted period to recovery. It would seem that more often than not weeks and even months of slow recovery of strength are required for what was considered a trifling illness. It is said occasionally in facile explanation of such events that there are psychologic grounds adequate to explain the phenomena. This may well be in certain circumstances, but the explanation is not fully adequate in the instance of the active, effective person who undergoes this period of post-infectious asthenia and returns finally to his full and active life.

It is not intended here to belittle the emotional factors which may play a determining role in weakness in general. It seems clear that in a large number of instances these factors are paramount; in all patients they contribute influences which may be either detrimental or beneficial. On many occasions the dissection of the pathophysiology of contractility from the pathophysiology of attitude is extremely difficult to accomplish, if indeed it is necessary at all.

RECAPITULATION

It was not intended that this be a review of the literature; rather it has been the purpose of this essay to indicate that disease of skeletal muscle is commonly encountered in the practice of medicine. In most instances it is secondary to remote causes. Often it is not in itself serious and happily responds with correction of the underlying disorder. In some cases, however, as in disuse atrophy associated with convalescence, it has an independent existence which is troublesome to the patient and yet which can be managed. In other instances, phenomena of skeletal muscle disease dominate the clinical picture, obscuring the fact that they are reactive responses to constitutional disease. Conversely, there are those diseases of muscle, primary in the sense that no remote cause has been recognized, and yet associated often with evidence of disease of other tissue so that they may at times masquerade as more familiar constitutional disease.

It remains challenging that skeletal muscle, so widely studied and understood at certain functional levels by physiologists and biochemists, continues to perplex the clinician by its behavior in these experiments of nature which are here called myopathies.

REFERENCES

1. Adams, R. D., Denny-Brown, D. and Pearson, C. M. Diseases of Muscle. A Study in Pathology. New York, 1953. P. B. Hoeber.
2. Andrus, S., Kass, E. H., Adams, R. D., Turner, F. C. and Feldman, H. A. Toxoplasmosis in the adult. *Arch. Int. Med.*, 89: 759, 1952.
3. Aring, C. D. and Cobb, S. The muscular atrophies and allied disorders. *Medicine*, 14: 77, 1935.
4. Baldwin, D., Robinson, P. K., Zierler, K. L. and Lilienthal, J. L., Jr. Interrelations of magnesium, potassium, phosphorus and creatine in skeletal muscle of man. *J. Clin. Investigation*, 31: 850, 1952.

5. Barnes, S. A myopathic family; with hypertrophic, pseudohypertrophic, atrophic and terminal (distal in upper extremities) stages. *Brain*, 55: 1, 1932.
6. Bell, J. The Treasury of Human Inheritance, vol. 4. London, 1943. Cambridge Univ. Press.
7. Benda, C. E. and Bixby, E. M. Urinary excretion of 17-ketosteroids in various conditions of oligophrenia correlated with some autopsy observations. *J. Clin. Endocrinol.*, 7: 503, 1947.
8. Biemond, A. and Daniels, A. P. Familial periodic paralysis and its transition into spinal muscular atrophy. *Brain*, 57: 91, 1934.
9. Brain, W. R. Exophthalmic ophthalmoplegia. *Quart. J. Med.*, 7: 293, 1938.
10. Bramwell, E. On the muscular dystrophies, sympathetic system and endocrine glands. *Lancet*, 2: 1103, 1925.
11. Brinkhous, K. M. and Warner, E. D. Muscular dystrophy in biliary fistula dogs; possible relationships to vitamin E deficiency. *Am. J. Path.*, 17: 81, 1941.
12. Brown, G. L. and Harvey, A. M. Congenital myotonia in the goat. *Brain*, 62: 341, 1939.
13. Brown, M. R., Currens, J. H. and Marchand, J. F. Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. *J. A. M. A.*, 124: 545, 1944.
14. Bywaters, E. G. L. Le Muscle (Ed: Schapira). Paris, 1952. L'Expansion Scientifique Francaise.
15. Cannon, P. R., Frazier, L. E. and Hughes, R. H. Influence of potassium on tissue protein synthesis. *Metabolism*, 1: 49, 1952.
16. Cannon, W. B. and Rosenblueth, A. The Supersensitivity of Denervated Structures. New York, 1949. Macmillan.
17. Caughey, J. E. and Brown, J. Dystrophia myotonica: an endocrine study. *Quart. J. Med.*, 19: 303, 1950.
18. Cowle, J. B. and Thorp, R. H. Action of cortisone on the polymerization of actin. *Nature*, London, 171: 1067, 1953.
19. Csapo, A. I. and Corner, G. W. The antagonistic effects of estrogen and progesterone on the staircase phenomenon in uterine muscle. *Endocrinology*, 51: 378, 1952.
20. Csapo, A. I. and Corner, G. W. The effect of estrogen on the isometric tension of rabbit uterine strips. *Science*, 117: 162, 1953.
21. Dalldorf, G. The lesions in the skeletal muscles in experimental scorbutus. *J. Exper. Med.*, 50: 293, 1929.
22. Danowski, T. S. Newer concepts of the role of potassium in disease. *Am. J. Med.*, 7: 525, 1949.
23. Darby, W. J., Ferguson, M. E., Furman, R. H., Lemley, J. M., Ball, C. T. and Meneely, G. R. Plasma tocopherols in health and disease. *Ann. New York Acad. Sc.*, 52: 328, 1949.
24. Denny-Brown, D. The nature of muscular diseases. *Canad. M. A. J.*, 67: 1, 1952.
25. Denny-Brown, D. and Foley, J. M. Evidence of a chemical mediator in myotonia. *Tr. A. Am. Physicians*, 62: 187, 1949.
26. Denny-Brown, D. and Nevin, S. The phenomenon of myotonia. *Brain*, 64: 1, 1941.
27. Denny-Brown, D. and Pennybacker, J. B. Fibrillation and fasciculation in voluntary muscle. *Brain*, 61: 311, 1938.
28. Derrick, E. H. Heat cramps and uraemic cramps, with special reference to their treatment with sodium chloride. *M. J. Australia*, 2: 612, 1934.
29. Dobyns, B. M. Studies on exophthalmos produced by thyrotropic hormone. II. Changes induced in various tissues and organs (including the orbit) by thyrotropic hormone and their relationship to exophthalmos. *Surg., Gynec. & Obst.*, 82: 290, 1946.
30. Dreyfus, J.-C., Schapira, G. and Schapira, F. Observations to be published.
31. Eccles, J. C. Disuse atrophy of skeletal muscle. *M. J. Australia*, 2: 160, 1941.
32. Eccles, J. C. Investigations on muscle atrophies arising from disuse and tenotomy. *J. Physiol.*, 103: 253, 1944.
33. Ellis, J. T. Studies on the nature and pathogenesis of muscular degeneration in cortisone-treated rabbits (abstr.). *Am. J. Path.*, 28: 542, 1952.
34. Engbaek, L. Investigations on the course and localisation of magnesium anesthesia. *Acta pharmacol. et toxicol.*, 4: 1, 1948.
35. Eyzaguirre, C., Folk, B. P., Zierler, K. L. and Lilienthal, J. L., Jr. Experimental myotonia and repetitive phenomena: the veratrinic effects of 2,4-dichlorphenoxyacetate (2,4-D) in the rat. *Am. J. Physiol.*, 155: 69, 1948.
36. Fenn, W. O. Physical Chemistry of Cells and Tissues (Ed: Höber). Philadelphia, 1945. Blakiston.
37. Ferrebee, J. W., Parker, D., Carnes, W. H., Gerity, M. K., Atchley, D. W. and Loeb, R. F. Certain effects of desoxycorticosterone; the development of "diabetes insipidus" and the replacement of muscle potassium by sodium in normal dogs. *Am. J. Physiol.*, 135: 230, 1941.
38. Finch, C. A., Sawyer, C. G. and Flynn, J. M. The clinical syndrome of potassium intoxication. *Am. J. Med.*, 1: 337, 1946.
39. Fischer, E. Le Muscle (Ed: Schapira). Paris, 1952. L'Expansion Scientifique Francaise.
40. Folk, B. P., Zierler, K. L. and Lilienthal, J. L., Jr. Unpublished observations.
41. Forbus, W. D. Pathologic changes in voluntary muscle. I. Degeneration and regeneration of the rectus abdominis in pneumonia. *Arch. Path.*, 2: 318, 1926.
42. Gerard, R. W. and Taylor, R. E. Muscle and nerve–physiologic orientation. *Am. J. Med.*, 15: 83, 1953.
43. Godman, G. C., Bunting, H. and Melnick, J. L. The histopathology of Coxsackie virus infection in mice. I. Morphologic observations with four different viral types. *Am. J. Path.*, 28: 223, 1952.
44. Goldstein, M. S., Ramey, E. R. and Levine, R. Relation of muscular fatigue in the adrenalectomized dog to inadequate circulatory adjustment. *Am. J. Physiol.*, 163: 561, 1950.
45. Gould, S. E. Trichinosis. Springfield, Ill., 1945. Charles C Thomas.
46. Greenman, L., Shaler, J. B. and Danowski, T. S. Biochemical disturbances and clinical symptoms during prolonged exchange resin therapy in

congestive heart failure. *Am. J. Med.*, 14: 391, 1953.

47. Hicks, S. P. Brain metabolism in vivo. II. The distribution of lesions caused by azide, malononitrile, plasmocid and dinitrophenol poisoning in rats. *Arch. Path.*, 49: 111, 1950.
48. Hines, H. M. Le Muscle (Ed: Schapira). Paris, 1952. L'Expansion Scientifique Francaise.
49. Hoagland, C. L. Currents in Biochemical Research (Ed: Green). New York, 1946. Interscience Publishers.
50. Hodgkin, A. L. The ionic basis of electrical activity in nerve and muscle. *Biol. Rev.*, 26: 339, 1951.
51. Holler, J. W. Potassium deficiency during treatment of diabetic acidosis. *J. A. M. A.*, 131: 1186, 1946.
52. Kilbourne, E. D. The Coxsackie viruses and human disease. *Am. J. M. Sc.*, 224: 93, 1952.
53. Krabbe, K. H. The myotonia acquisita in relation to the post-neuritic hypertrophies. *Brain*, 57: 184, 1934.
54. Kreutzer, F. L., Strait, L. and Kerr, W. J. Spontaneous myohemoglobinuria in man. *Arch. Int. Med.*, 81: 249, 1948.
55. Kugelberg, E. Electromyography in muscle dystrophies. *J. Neurol., Neurosurg. & Psychiat.*, 12: 129, 1949.
56. Lanari, A. Los musculos estriados en el hipotiroidismo. *Medicina*, Buenos Aires, 7: 197, 1947.
57. Landau, W. M. The essential mechanism in myotonia. *Neurology*, 2: 369, 1952.
58. Levy, R. I. Unpublished observations.
59. Lewis, M. R. Rhythmical contraction of the skeletal muscle tissue observed in tissue cultures. *Am. J. Physiol.*, 38: 153, 1915.
60. Lilienthal, J. L., Jr. The Musculo-skeletal System. New York, 1952. Macmillan.
61. Lilienthal, J. L., Jr., Zierler, K. L., Folk, B. P., Buka, R. and Riley, M. J. A reference base and system for analysis of muscle constituents. *J. Biol. Chem.*, 182: 501, 1950.
62. Ling, G. Phosphorus Metabolism, vol. II, p. 748. Baltimore, 1952. Johns Hopkins Press.
63. Ling, G. and Gerard, R. W. External potassium and the membrane potential of single muscle fibres. *Nature, London*, 165: 113, 1950.
64. Maas, O. and Paterson, A. S. The identity of myotonia congenita, dystrophia myotonica, and paramyotonia. *Brain*, 62: 198, 1939.
65. McArdle, B. Myopathy due to a defect in muscle glycogen breakdown. *Clin. Sc.*, 10: 13, 1951.
66. McCance, R. A. Medical problems in mineral metabolism. III. Experimental human salt deficiency. *Lancet*, 230: 823, 1936.
67. Milhorat, A. T. and Wolff, H. G. Studies in diseases of muscle. v. Metabolism of creatine and creatinine in myotonia congenita, myotonia atrophica, amyotonia congenita, dystonia musculorum deformans and paralysis agitans. *Arch. Neurol. & Psychiat.*, 40: 680, 1938.
68. Minot, A. S., Frank, H. and Dziewiatkowski, D. Occurrence of pentose- and phosphorus-containing complexes in the urine of patients with progressive muscular dystrophy. *Arch. Biochem.*, 20: 394, 1949.
69. Mirski, A. and Wertheimer, E. Muscle action and glycogen phosphorolysis. *Biochem. J.*, 36: 221, 1942.
70. Muntwyler, E., Mellors, R. C., Mautz, F. R. and Mangun, G. H. Electrolyte and water equilibria in the dog. II. Electrolyte and water exchange between skeletal muscle and blood in adrenal insufficiency. *J. Biol. Chem.*, 134: 367, 1940.
71. Nevin, S. Two cases of muscular degeneration occurring in late adult life, with a review of the recorded cases of late progressive muscular dystrophy (late progressive myopathy). *Quart. J. Med.*, 5: 51, 1936.
72. O'Leary, P. A. and Waisman, M. Dermatomyositis: a study of 40 cases. *Arch. Dermat. & Syph.*, 41: 1001, 1940.
73. Pappenheimer, A. M. On Certain Aspects of Vitamin E Deficiency. Springfield, Ill., 1948. Charles C Thomas.
74. Peters, J. P. Diseases of Metabolism (Ed: Duncan). Philadelphia, 1952. Saunders.
75. Pinelli, P. and Buchthal, F. Muscle action potentials in myopathies with special regard to progressive muscular dystrophy. *Neurology*, 3: 347, 1953.
76. Poncher, H. G. and Woodward, H. Pathogenesis and treatment of myotonia congenita. *Am. J. Dis. Child.*, 52: 1065, 1936.
77. Rabinovitch, R., Gibson, W. C. and McEachern, D. Neuromuscular disorders amenable to wheat germ therapy. *J. Neurol., Neurosurg. & Psychiat.*, 14: 95, 1951.
78. Rowe, W. P. Propagation of group A Coxsackie viruses in denervated adult mouse muscle. *Science*, 117: 710, 1953.
79. Schapira, G. and Dreyfus, J.-C. Le Muscle (Ed: Schapira). Paris, 1952. L'Expansion Scientifique Francaise.
80. Sexton, R. C., Jr., Eyles, D. E. and Dillman, R. E. Adult toxoplasmosis. *Am. J. Med.*, 14: 366, 1953.
81. Shank, R. E., Gilder, H. and Hoagland, C. L. Studies on diseases of muscle. I. Progressive muscular dystrophy; a clinical review of forty cases. *Arch. Neurol. & Psychiat.*, 52: 431, 1944.
82. Sheldon, W. H. Lesions of muscle in spirochetal jaundice (Weil's disease; spirochetosis icterohemorrhagica). *Arch. Int. Med.*, 75: 119, 1945.
83. Shy, G. M. and McEachern, D. The clinical features and response to cortisone of menopausal muscular dystrophy. *J. Neurol., Neurosurg. & Psychiat.*, 14: 101, 1951.
84. Sibley, J. A. and Lehninger, A. L. Aldolase in the serum and tissues of tumor-bearing animals. *J. Nat. Cancer Inst.*, 9: 303, 1948.
85. Steinbach, H. B. Intracellular inorganic ions and muscle action. *Ann. New York Acad. Sc.*, 47: 849, 1947.
86. Sylverton, J. T. and Slavin, H. B. Human toxoplasmosis. *J. A. M. A.*, 131: 957, 1946
87. Szent-Györgyi, A. Chemistry of Muscular Contraction. New York, 1951. Academic Press.
88. Talbott, J. H. Periodic paralysis: a clinical syndrome. *Medicine*, 20: 85, 1941.

89. Talbott, J. H. and Michelsen, J. Heat cramps. A clinical and chemical study. *J. Clin. Investigation*, 12: 533, 1933.
90. Tarail, R., Hacker, E. S. and Taymor, R. The ultrafiltrability of potassium and sodium in human serum. *J. Clin. Investigation*, 31: 23, 1952.
91. Tyler, F. H. and Stephens, F. E. Studies in disorders of muscle. II. Clinical manifestations and inheritance of facioscapulohumeral dystrophy in a large family. *Ann. Int. Med.*, 32: 640, 1950.
92. Tyler, F. H. and Stephens, F. E. Studies in disorders of muscle. IV. The clinical manifestations and inheritance of childhood progressive muscular dystrophy. *Ann. Int. Med.*, 35: 169, 1951.
93. Tyler, F. H., Stephens, F. E., Gunn, F. D. and Perkoff, G. T. Studies in disorders of muscle. VII. Clinical manifestations and inheritance of a type of periodic paralysis without hypopotassemia. *J. Clin. Investigation*, 30: 492, 1951.
94. Vicale, C. T. The diagnostic features of a muscular syndrome resulting from hyperparathyroidism, osteomalacia owing to renal tubular acidosis, and perhaps to related disorders of calcium metabolism. *Tr. Am. Neurol. A.*, 74: 143, 1949.
95. Victor, J. Metabolic and irritability changes in nutritional myopathy of rabbits and ducks. *Am. J. Physiol.*, 108: 229, 1934.
96. Waring, J. J., Ravin, A. and Walker, C. E. Studies in dystrophia myotonica. II. Clinical features and treatment. *Arch. Int. Med.*, 65: 763, 1940.
97. Watson, C. W. Familial periodic paralysis. Report of a case showing no changes in serum potassium levels with a description of electroencephalographic findings. *Yale J. Biol. & Med.*, 19: 127, 1946.
98. Wohlfart, G. Dystrophia myotonica and myotonia congenita: histopathologic studies with special reference to changes in the muscles. *J. Neuropath. & Exper. Neurol.*, 10: 109, 1951.
99. Zenker, F. A. Über die Veränderungen der willkürlichen Muskeln im Typhus abdominalis. Erlangen, 1863. A. E. Junge.
100. Zierler, K. L. Muscular wasting of obscure origin and the thyroid gland. *Bull. Johns Hopkins Hosp.*, 89: 263, 1951.
101. Zierler, K. L., Folk, B. P., Eyzaguirre, C., Jarcho, L. W., Grob, D. and Lilienthal, J. L., Jr. On certain effects of alpha-tocopheryl phosphate on oxidative mechanisms of striated muscle. *Ann. New York Acad. Sc.*, 52: 180, 1949.
102. Zierler, K. L., Folk, B. P., Magladery, J. W. and Lilienthal, J. L., Jr. On creatinuria in man. The roles of the renal tubule and of muscle mass. *Bull. Johns Hopkins Hosp.*, 85: 370, 1949.
103. Zierler, K. L., Levy, R. I. and Lilienthal, J. L., Jr. On the mechanism of action of α-tocopheryl phosphate, with special reference to carbohydrate metabolism of striated muscle. III. Inhibition of insulin-induced glycogenesis in isolated rat diaphragm. *Bull. Johns Hopkins Hosp.*, 92: 41, 1953.

Case Reports

A Simultaneous Study of Glycine-N^{15} Incorporation into Uric Acid and Heme, and of Fe^{59} Utilization, in a Case of Gout Associated with Polycythemia Secondary to Congenital Heart Disease*

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THE case to be described combined marked polycythemia secondary to congenital heart disease with advanced secondary gout and thus offered an unusual opportunity to investigate the interrelationships between purine, porphyrin and iron metabolism in accelerated erythropoiesis. The study was carried out by administering glycine-N^{15} and Fe^{59} as metabolic tracers.

Glycine is a precursor of purines and nucleic acids in biosynthesis, carbons 4 and 5 of the purine molecule being derived from the carboxyl and methylene carbons, respectively, of glycine, and nitrogen 7 from glycine nitrogen.[1] By measuring the rate of incorporation of glycine-N^{15} into uric acid it is possible to make certain deductions concerning intermediary pathways of purine metabolism. This method has already been applied to study of uric acid biosynthesis in classical gout,[2–4] an inborn error of metabolism which may be regarded as the primary form of the disease.[5] The present study was designed to extend the observations to an acquired form of the disorder, gout secondary to polycythemia and, for reasons stated elsewhere,[5] presumably of different metabolic origin.

Glycine is a precursor also in the biosynthesis of protoporphyrin, the methylene carbon and nitrogen being utilized in formation of the four pyrrole rings, the methylene carbon contributing in addition to elaboration of the methene bridges.[6–8] By concurrently studying the rate of incorporation of glycine-N^{15} into heme in this case it was possible to make parallel observations on the fate of glycine in two divergent metabolic pathways of special interest. A similar experiment in a normal human subject has been described by Shemin and Rittenberg.[9,10] Data on the rate of incorporation of isotope-labeled glycine into heme are available in polycythemia vera[11,12] but not in secondary polycythemia.

It has been demonstrated that in the presence of normal iron stores the disappearance rate of radioiron from the plasma and its subsequent utilization by the red cells can be directly correlated with the erythropoietic activity of the marrow.[13–17] As a further index to the erythropoietic activity of our patient, the rate of turnover of iron in the plasma and red cells was therefore measured by concurrent use of Fe^{59}. The data obtained are of additional interest in relation to figures recorded in normal human subjects,[15–17] in polycythemia vera[15–17,20] and in polycythemia secondary to anoxemia.[18–20]

CASE REPORT

E. F. (M. S. H. No. 642,387), a fifty year old man, was referred to us by Dr. Nathan Rosenthal in June, 1952, for special studies.

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The patient was a "blue baby" at birth and cyanosis had persisted throughout life. Marked clubbing of the fingers and toes developed early in childhood. He denied "squatting" or equivalent attitudes as a child. His physical activities had always been hampered by breathlessness and fatigue on exertion but he was able to complete his schooling and had since carried on a fairly active law practice. This had become increasingly difficult in recent years.

At age twenty he bled profusely after extraction of a tooth, and upon examination of the blood, polycythemia was noted. This had been treated over the years by periodic phlebotomies (the last, ten weeks and again six weeks prior to hospital admission), with temporary lowering of the erythrocyte count and partial relief of symptoms. In 1951 he received a course of P^{32} therapy but with no marked or sustained effect. Dr. Rosenthal's records indicated recent red cell counts in excess of 8 million, hemoglobin 23 gm., hematocrit 78 per cent.

At age thirty-five he suffered a profuse pulmonary hemorrhage and was confined to his home for six months. This episode was associated with non-productive cough which persisted for a long time. In 1950 there was an episode of syncope with unconsciousness for some six hours. This was attributed to cerebral thrombosis complicating secondary polycythemia. Except for spasmodic twitching of the right side of the face and the right eyelid, there were no sequelae.

Since the age of forty he had noted marked ankle edema, more evident at the end of the day and somewhat relieved during the night, particularly with elevation of the leg. He had never taken digitalis.

The first indication of gout came at the age of thirty-five. There was sudden onset of painful swelling of the ankle which subsided spontaneously. Typical acute gouty attacks recurred, at first every five to six months, then with increasing frequency. The ankles, knees, wrists and elbows were particularly affected. In recent years he had rarely been altogether free of pain, suffering major acute gouty attacks almost every month. These responded to colchicine. Early in his course residual stiffness of joints developed, particularly of the fingers and knees, and at age thirty-seven tophi appeared on the lobes of the ears. In the past seven years tophaceous deposits had developed in the hands, feet and elbows, with rapid recent increase in size and number. These tophi occasionally discharged a thick creamy material in which uric acid crystals had been identified. There were no complaints referable to urinary urate calculi. There was no familial history of gout.

Upon admission to the Mount Sinai Hospital on June 11, 1952, the patient presented a striking appearance. A slight man of medium height and fairly well nourished, he was obviously chronically ill and constantly in some discomfort. There was dyspnea even at rest, with marked cyanosis particularly of the lips, nose, tongue, conjunctivae, ear lobes, finger and toenails. Large tophaceous deposits were visible on the ears, left hand, right elbow and both feet. (Figs. 1 to 4.) Because of stiffness and deformity of the feet, the gait was slow and labored. There was frequent twitching of the right side of the face. The patient was afebrile, the pulse rate was 48 and irregular, the respiratory rate was 18 and the blood pressure 160/100–110.

Closer examination brought out additional findings of interest. The eyes were suffused, as in marked polycythemia, and funduscopy revealed striking congestion of the fundal veins. The neck veins were obviously distended. The chest was asymmetric, with a slight precordial bulge on the right side. The anteroposterior diameter of the thorax appeared to be increased and some kyphosis was present. Percussion of the chest revealed no impairment of resonance but crackling rales were present at the base of both lungs, chiefly on the right side posteriorly.

The heart appeared on percussion to be moderately enlarged, chiefly to the right. No apical thrust or impulse could be felt on the left. The heart sounds were of good quality but were heard more distinctly to the right than to the left of the sternum. The second sound in the aortic area was loud and snapping. The second sound in the pulmonic artery area was audible but not accentuated. A very loud, harsh, prolonged systolic murmur was present over the entire precordium with maximal intensity over the second intercostal space on the right; no diastolic murmur was heard.

Upon examination of the abdomen no liver edge could be felt in the right upper quadrant and there was dullness to percussion over the left upper quadrant. The tip of the spleen could be felt 1½ fingerbreadths below the costal margin on the right. No other masses were palpable; no ascites was present. The lower extremities showed marked cyanosis, edema of the ankles,

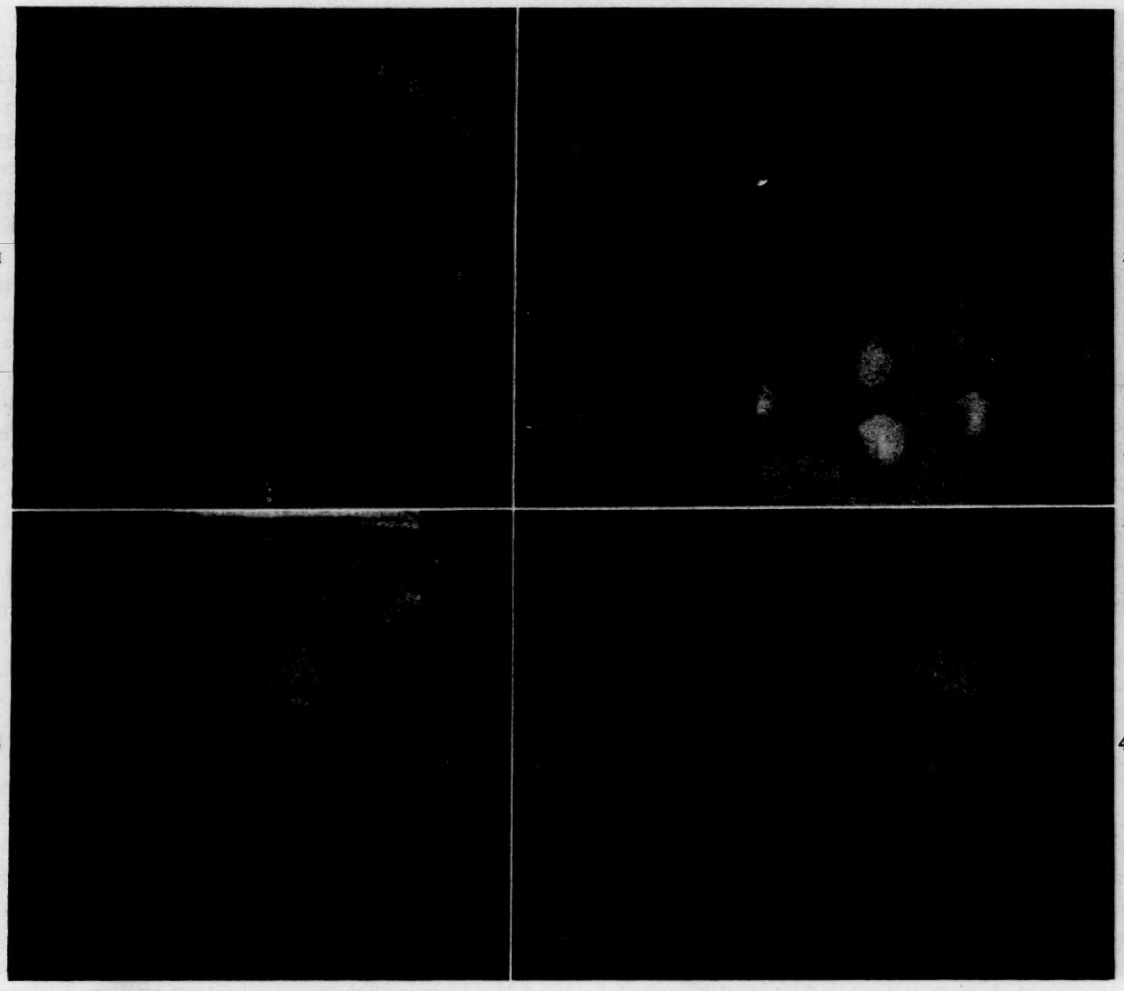

FIG. 1. Case E. F., right ear showing tophi.

FIG. 2. Case E. F., left hand: note marked clubbing of fingers and large tophaceous deposit involving index finger.

FIG. 3. Case E. F., right elbow showing large tophaceous deposit in olecranon bursa and smaller deposits along the ulnar border of the forearm.

FIG. 4. Case E. F., view of feet showing marked clubbing of toes with edema and extensive tophaceous deposits at base of great toe of both feet.

clubbing of the toes and the tophaceous deformities of the feet already mentioned.

X-ray examination of the chest gave evidence of an old, healed tuberculous lesion in the right upper lobe, probably explaining the period of cough and hemoptysis fifteen years before. Situs inversus was present. The gastric air bubble was visible under the right leaf of the diaphragm; the liver density was seen on the left side. The heart was globular in outline, not markedly enlarged (Fig. 5); its precise position, whether dextro- or levocardia, could not be ascertained by study in various projections. There was a right aortic arch and the descending aorta was visualized to the right of the midline. No abnormality of the pulmonary vessels was apparent. Further study by angiocardiography and cardiac catheterization was refused by the patient. The extent of transposition of the heart chambers and great vessels was therefore never precisely established.

Electrocardiograms revealed complete A-V block with an auricular rate of 78/min.; the ventricular rate was irregular due to two idioventricular pacemakers acting at different rates. P waves were very tall, broad and bifid, indicating auricular hypertrophy. RS-T was de-

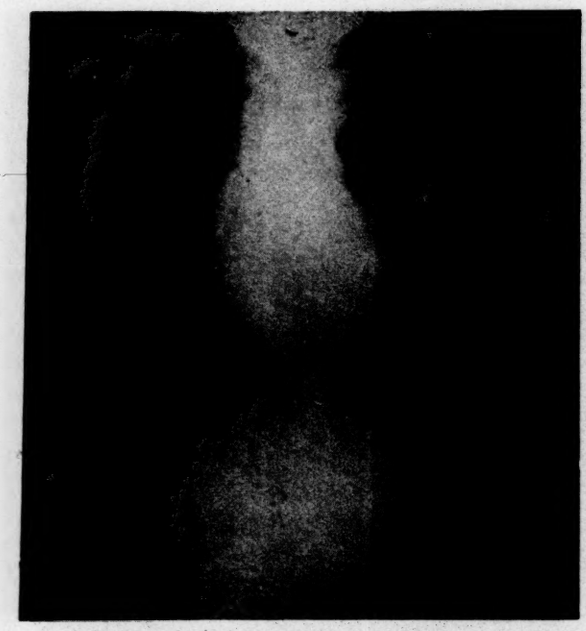

FIG. 5. Case E. F., 2-meter, posterior-anterior x-ray film of chest. The heart is globular in configuration but not markedly enlarged. The aortic arch is seen on the right side. The pulmonary vessels appear to be of normal configuration. The stomach bubble is visualized on the right side.

pressed in leads II, III, AVF, V_4 and V_5. T was diphasic in leads III, AVF and V_4, inverted in leads V_1 to V_3. The venous pressure was 120 mm., rising to 190 mm. on pressure in the left upper quadrant. The ether circulation time was 30 seconds, decholin circulation time 45 seconds.

The red cell count was 7.71 million (subsequently 7.43 and 7.08 million), hemoglobin 21.4 to 22.8 gm. on various occasions, hematocrit 76 per cent, white cell count 5,750 with normal differential, platelets 120,000. The reticulocyte count was 1 per cent; no normoblasts were present. Bleeding and clotting time and clot retraction were normal. Sternal bone marrow aspiration revealed marked erythroid hyperplasia with a myeloid/erythroid ratio of 0.6:1. The serum iron was 168 γ per cent. The plasma volume as determined by the radioactive iron method was 1,910 cc.; the red cell volume, assuming a corrected hematocrit of 68.6 per cent, was 4,170 cc.; the total blood volume was 6,080 cc. (90 cc./kg. body weight).

The urine had a specific gravity of 1.006, showed 2–4 + albumin consistently and was negative for sugar; the sediment contained a few red and white cells, with occasional hyaline and granular casts per high power field. Phenolsulfonphthalein test: 52 per cent excretion in two hours.

The serum uric acid ranged between 9.8 and 11.2 mg. per cent; glucose 97 mg. per cent; urea nitrogen 22 mg. per cent; creatinine 2 mg. per cent; carbon dioxide content 37 vol. per cent; albumin 4.2 gm. per cent, globulin 4.1 gm. per cent; total cholesterol 323 mg. per cent; alkaline phosphatase 9 King-Armstrong units.

X-rays of the joints showed punched-out lesions in areas adjacent to the proximal interphalangeal joints of the right thumb and the second and fourth fingers of the left hand, with associated soft tissue swellings. (Fig. 6.) There was marked destruction of bone in the region of the metatarsophalangeal joint of the great toe of both feet, particularly on the left. (Fig. 7.) Surrounding these areas were large swellings of soft tissue.

Putting together the implications of the history and findings in this patient, it seems evident that a large right-to-left shunt was present from birth due to a congenital anomaly of the heart and great vessels. The nature of this anomaly was never precisely determined but the case may fall into the category of situs inversus of the abdominal viscera with levocardia, which may be associated with complex malformations.[21] The accompanying marked cyanosis was associated with the development of severe secondary polycythemia; and the appearance of gout appeared to be related to the polycythemia.

Since there was indication of congestive failure, the patient was put to bed and digitalized. Prophylactic colchicine, 0.5 mg. twice daily, was administered to avert an attack of acute gouty arthritis. By way of preparation for the metabolic studies, the patient was given a constant, meat-free, 1,800 calorie diet, low in purines and fat and containing 67 gm. protein per day.

The patient was maintained on the diet indicated for several days of control observation prior to administration of the isotope preparations, and thereafter throughout the experiment. The serum uric acid was 10.2 mg. per cent and the basal urinary uric acid excretion was 317 mg./24 hours in the control period. These and subsequent uric acid determinations were made by a modification of the method of Buchanan, Block and Christman[22] incorporating the use of uricase, arsenophosphotungstic acid and urea cyanide-carbonate.

On the morning of June 14th, while in the

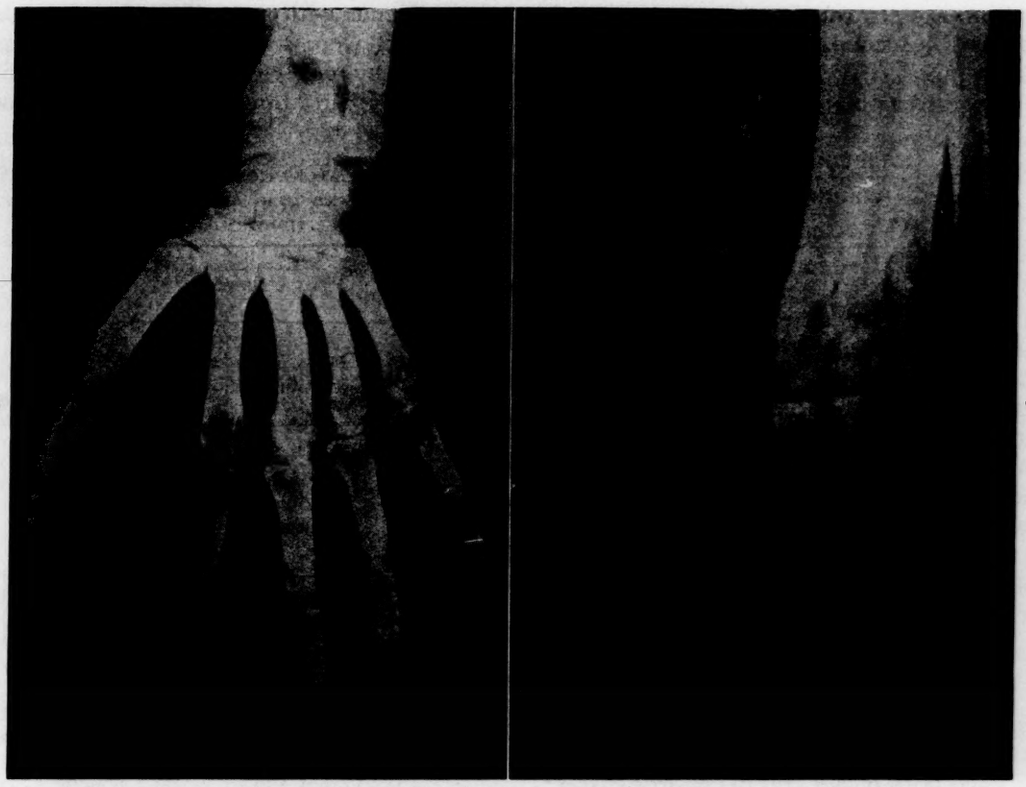

FIG. 6. Case E. F., roentgenogram of left hand showing several "punched-out" areas of bone lucency and a large soft-tissue shadow (tophaceous deposit) of index finger.

FIG. 7. Case E. F., roentgenogram of left foot showing extensive destruction of metatarsophalangeal joint of great toe, with surrounding soft tissue swelling, due to a large tophaceous deposit.

fasting state, the patient was given by mouth, in a single dose, 6.75 gm. (0.1 gm./kg. body weight) N^{15}-labeled glycine. This was prepared by the method of Schoenheimer and Ratner[23] from potassium phthalimide containing approximately 60 atom per cent excess N^{15}. The isolation and purification of uric acid from twenty-four-hour urine collections and the procedures for mass spectrometric analysis of the urinary uric acid were conducted as described elsewhere.[2]

About three hours prior to glycine-N^{15} feeding approximately 10.3 microcuries of Fe^{59}, as ferric-β-1-globulinate, were injected intravenously. The radioiron was obtained as ferric chloride from the Atomic Energy Commission and converted to the ferric-59-β-1-globulinate on the day of injection.[16] Serial samples of blood were taken with heparinized equipment 10, 20, 30, 45, 60, 75, 100, 106 and 120 minutes after injection, and at twelve-hour intervals thereafter for the first three days. Samples were then obtained daily for the remainder of the first week and at longer intervals thereafter. The studies unfortunately could not be continued beyond fifty-six days.

Blood specimens so obtained were centrifuged, the plasma removed and the remaining red cells washed twice with saline solution and made up to the original volume. An aliquot was removed for determination of red cell radioactivity and the remainder (about 25 cc.) was used for preparation of crystalline heme. Radioactivity of the plasma and red cell hemolysate was measured directly by means of a well-type, sodium iodide (thallium-activated) scintillation crystal (Harshaw), using a conventional scaling unit. All specimens were counted for a total of 10,240 counts. The half-time of plasma Fe^{59} disappearance, rates of plasma iron and red cell turnover/day and the rate of hemoglobin renewal/day were calculated according to Huff et al.[15] The blood volume was determined from the radioactivity of the first four plasma specimens obtained after the injection of ferric-59-β-1-globulinate. The values were plotted on a semi-log graph and a smooth curve drawn through

these points was extrapolated back to give the counts per cc.-second at zero time (t_0). The plasma volume (P.V.) and red cell volume (R.C.V.) were calculated from the formulas:

$$\text{P.V.} = \frac{\text{(total counts/sec.) injected}}{\text{(counts/cc.-sec.) at } t_0}$$

$$\text{R.C.V.} = \frac{\text{P.V.} \times \text{corrected hematocrit}}{100 - \text{corrected hematocrit}}$$

Serum iron was determined by the method of Barkan and Walker.[24] Hematocrits were checked by the Wintrobe technic and corrected for plasma trapping by the factor 0.915.

Heme was isolated from the red cells of blood specimens obtained at twelve-hour (later longer) intervals by the procedure outlined by Fischer.[25] Preparatory to mass spectrometric analysis the heme was purified by solution in pyridine-chloroform mixture and reprecipitation with hydrochloric-acetic acid.

RESULTS AND COMMENT

Incorporation of Glycine-N^{15} into Uric Acid. The biosynthesis of purines and their ribotides has been studied both *in vivo* and in cell-free extracts of liver, and it has been shown[1,26–29] that glycine, formate, ammonia, CO_2 and ribose-1-phosphate combine to yield 4-amino-5-imidazolecarboxamide ribotide. Upon further formylation this product gives inosinic acid which, upon amination, yields adenylic acid. Uric acid in man is presumed to arise chiefly by the xanthine oxidase catalyzed oxidation of the purine moieties, xanthine and hypoxanthine, derived from the body nucleotides and nucleic acids. As previously indicated, carbon atoms 4 and 5 of the uric acid so formed arise specifically from the carboxyl and α-carbon atoms of glycine and nitrogen atom 7 is likewise derived from glycine.

When glycine-N^{15} is fed in the presently employed dosage to normal human subjects, 30 to 50 per cent of the ingested N^{15} can be recovered in the urine in the succeeding ten days, some 0.3 per cent appearing in the urinary uric acid. The isotope abundance in urinary uric acid rapidly rises to a maximum value on the second to fourth day after administration of glycine-N^{15} and thereafter slowly declines. (Fig. 8.) When glycine containing approximately 60 atom per cent excess N^{15} was fed,[2–4,10] this maximum had a value of about 0.1 atom per cent excess N^{15}.

When the same dose of glycine-N^{15} was fed to patients with primary gout, two differing responses were secured. Of four such patients studied by us[2,3] two excreted uric acid containing N^{15} in abundance similar to those seen in normal subjects. (Fig. 8.) These two patients, when maintained on basal purine-poor diets, had been found to excrete normal quantities of uric acid daily. In two other patients the peak

TABLE I
DATA ON INCORPORATION OF GLYCINE-N^{15} INTO URINARY TOTAL AND URIC ACID NITROGEN, AND INTO HEME, IN CASE E. F.

Day of Experiment	Urinary N^{15}				Heme N^{15} (atom %)
	Daily Excretion		Cumulative Excretion		
	Total N	Uric Acid N (atom %)	Total N	Uric Acid N (% of N^{15} fed)	
0.5					0.0014
1	2.417	0.0243	12.55	0.00275	0.0078
1.5					0.0238
2	1.041	0.0507	19.20	0.00989	0.0366
2.5					0.0566
3	0.687	0.0810	23.70	0.0224	0.1153
4	0.400	0.0980	26.49	0.0375	0.1081
5	0.212	0.1091	28.09	0.0499	0.1196
6	0.156	0.1162	29.18	0.0663	0.1160
7	0.138	0.1243	30.17	0.0827	0.1353
8	0.115	0.1293	30.97	0.0975	
9	0.101	0.1376	31.70	0.1160	0.1449
10	0.088	0.1403	32.29	0.1349	
11	0.092	0.1375	32.95	0.1625	0.1515
12	0.071	0.1333	33.37	0.1819	
13					0.1499
14	0.071	0.1303			
15	0.067	0.1227			
16	0.057				
17	0.055	0.1131			
18	0.059	0.1129			
19	0.058				
20	0.051	0.1016			
21	0.040	0.0948			
22	0.037	0.0931			
23	0.035	0.0895			
24	0.036	0.0790			0.1683
25	0.036	0.0827			
26		0.0847			
27		0.0789			
28		0.0810			
31					0.1625
38					0.1529
56					0.1331

enrichment of uric acid with N^{15}, occurring within two days, was three to five times as high as was seen in the normal subjects, and was followed by a rapid decline in N^{15}. (Fig. 8.) The basal urinary excretion of uric acid in the latter two patients was well in excess of normal. This finding has been interpreted to indicate that in such gouty patients there is excessive and direct synthesis of uric acid from metabolic precursors by routes which by-pass the large and sluggish purine reservoir of the nucleic acids.[2,3]

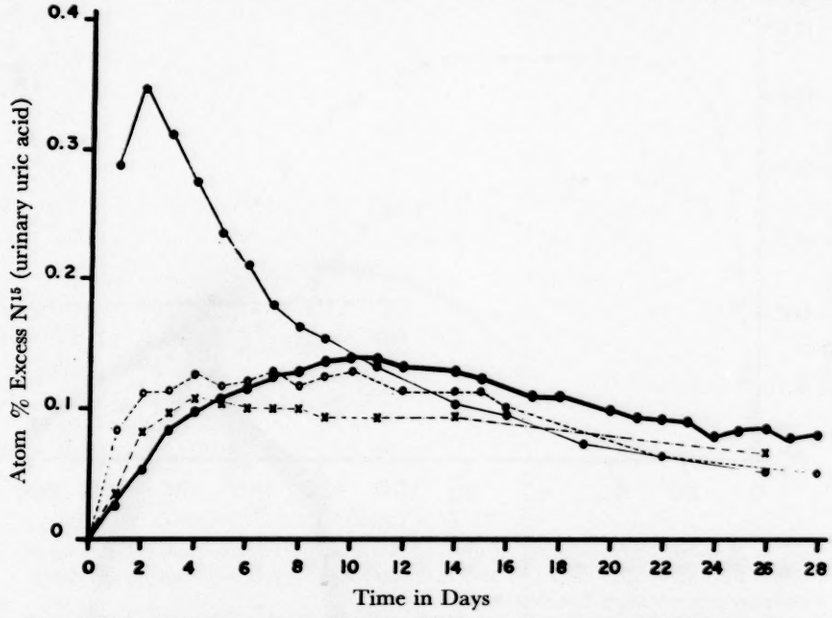

FIG. 8. Rate of incorporation of glycine-N^{15} into urinary uric acid in normal and gouty subjects. Broken line connecting crosses—normal man; broken line connecting open dots—gouty subject with urinary uric acid excretion within normal limits. Unbroken line connecting open dots—gouty subject regularly excreting excessive quantities of uric acid in the urine; unbroken heavy line connecting solid dots—Case E. F. See text for discussion of results.

In Case E. F., the subject of the present study, the time course of N^{15} abundance in urinary uric acid was quite different from those observed either in normal subjects or in patients with primary gout studied thus far. In this case the urinary uric acid continued to become progressively enriched with N^{15} until the tenth day, after which a decline ensued. (Table 1, Fig. 8.) This finding suggests an enhancement in this patient of some process whereby glycine of the diet contributes its nitrogen to uric acid, the entire process occurring within a week or more. It is assumed that this process is the incorporation of glycine into the purines contained within red cell precursors and, as the erythrocytes mature, the subsequent elimination of nucleic acids and oxidation of purines contained therein to uric acid. The time interval between ingestion of glycine-N^{15} and the peak of the uric acid N^{15} time course is believed to be related to the lapse of time between incorporation of glycine into the purines of the red cell precursors and the final disappearance of tagged nucleic acids from such cells. Presumably the abnormality found in glycine-N^{15} incorporation into uric acid in Case E. F. is related to the abnormally great turnover of nucleic acids characterizing the polycythemic reaction of this patient. Laster and Muller[29a] have observed a similar delay in the maximum of uric acid N^{15} concentration in another blood dyscrasia, agnogenic myeloid metaplasia, associated with gout. In this subject the maximum occurred on the fifteenth day after ingestion of glycine-N^{15}.

Incorporation of Glycine-N^{15} into Heme. When glycine N^{15} is fed to normal human subjects, heme obtained from circulating erythrocyte hemoglobin contains a significant concentration of the isotope within a matter of hours.[11] Maximum levels of isotope concentration are reached around the thirtieth day, and these are maintained for about another thirty days;[11,30] thereafter a decline sets in which is slow at first,

more rapid after about 100 days, then levels off from the 160th day. (Fig. 9.)

The early appearance of some isotope-labeled red cells in the circulating blood following ingestion of glycine-N^{15} may be attributed to rapid biosynthesis of heme by such red cells as normal.[11] From these curves it may be deduced that the excessive number of erythrocytes in polycythemia vera is not due to prolongation of the average life span of the red cell but to a more than two-fold increase in the rate of red cell and hemoglobin production. Similar con-

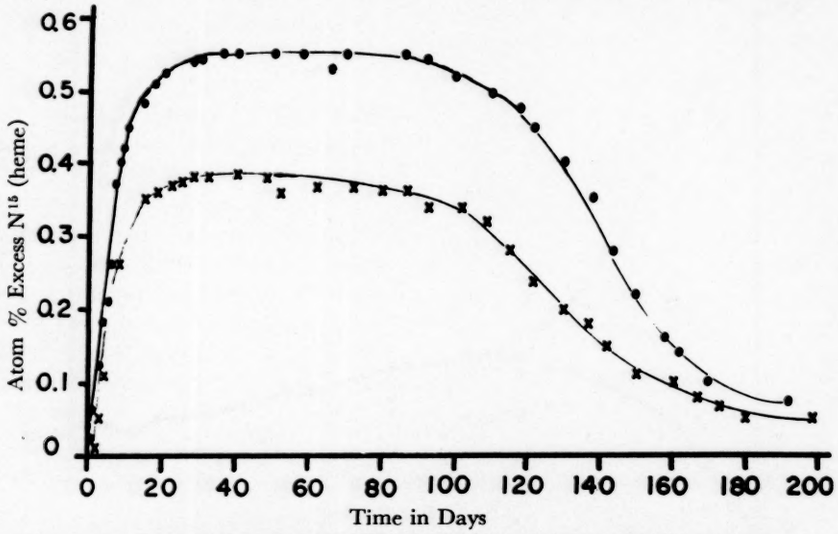

FIG. 9. Rate of incorporation of glycine-N^{15} into circulating red cell heme in normal human subject (crosses) and in a case of polycythemia vera (solid dots). Curves reprinted from London et al.[11]

are almost mature and ready for early release from the marrow into the peripheral circulation.[31] The ascending portion of the curve (Fig. 9) reflects the liberation of more and more isotopically labeled red cells into the circulating blood. After a few days the isotope abundance in heme precursors has fallen to low values and erythrocytes formed from this point on are poor in isotope. The red cells destroyed during this period are in general devoid of isotope, being the senescent erythrocytes released prior to isotope ingestion. With little isotope entering or leaving the heme of the circulating red cells, the isotope abundance in circulating red cell heme remains sensibly constant, as indicated by the plateau segment of the curve. Only when the labeled red cells break down does the isotope abundance in heme fall rapidly. On the basis of the time interval between the ascending and descending limbs of the curve, the mean life span of the normal human erythrocyte has been calculated to be about 120 days,[11,30] a figure in agreement with estimates made by the Ashby technic.[32–34]

Corresponding experiments in polycythemia vera have yielded curves identical with the clusions have been reached by Merskey[34] and by Elwood and de Wardener[35] using the Ashby technic. However, Berlin et al.[12] in studies on glycine-C^{14} incorporation into heme noted a sharp rise and fall in the specific activity of hemoglobin obtained within the first fifteen days of the experiment and consider that the red cell population in polycythemia vera contains an admixture of erythrocytes, some short-lived, others with normal survival periods. It is of interest that increased turnover of hemoglobin and erythrocytes in the face of a normal red cell life span would appear to involve increased excretion of pigments derived from hemoglobin breakdown but studies of urobilinogen excretion in polycythemia have revealed lower values than expected.[36] The implications of this discrepancy are obscure.

In Case E. F. the rate of incorporation of glycine-N^{15} into heme did not deviate significantly from the normal, the findings in this instance of secondary polycythemia thus corresponding with those in polycythemia vera. As indicated in Table 1 and Figure 10, significant concentrations of isotope-labeled heme appeared quickly in the circulating red cells and the

abundance of N^{15} rapidly increased, reaching a peak of about 0.17 atom per cent excess N^{15} at about the twenty-fourth day. Thereafter the curve shows a slow decline to about 0.13 atom per cent excess N^{15} on the fifty-sixth day when the experiment had to be terminated due to circumstances beyond our control. This decline appeared to be somewhat more rapid than had been found in normal subjects or in polycythemia vera. It will be noted that in the specimens collected at twelve-hour intervals during the first three days there is no definite indication of a short-lived component such as was described by Berlin et al.[12] using C^{14}-labeled glycine in patients with polycythemia vera. Because of the short duration of the experiment the average life span of the red cells in this case of secondary polycythemia could not be established.

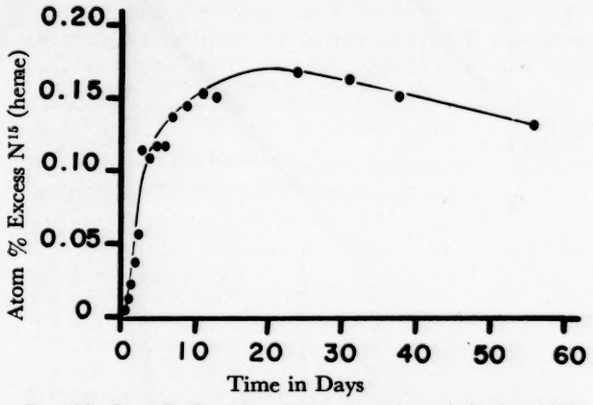

FIG. 10. Case E. F., rate of incorporation of glycine-N^{15} into circulating red cell heme; there is no essential difference from the findings in normal man and in polycythemia vera.

Utilization of Fe^{59}. The half-time ($T_{½}$) of disappearance from the plasma of intravenously injected ferric-59-β-1-globulinate averages 90 minutes (range 70 to 120 minutes) in normal human subjects.[16] In diseases characterized by decreased erythropoiesis the plasma Fe^{59} disappearance time is prolonged, commonly exceeding 200 minutes in chronic aplastic anemia, for example. In diseases associated with increased erythropoietic activity injected Fe^{59} disappears from the plasma more rapidly than normal.[15–17] Thus in polycythemia vera the $T_{½}$ has been found to be shortened to 11 to 60 minutes[15–17] and in polycythemia secondary to the anoxemia of high altitude the $T_{½}$ for plasma Fe^{59} disappearance was 30 to 60 minutes.[18,19]

In Case E. F. the initial half-time of disappearance of plasma Fe^{59} (Table II) was 31 minutes, a reflection of greatly increased erythropoietic activity in view of the normal serum iron of 168γ per cent. It will be noted in Figure 11 that the curve of plasma Fe^{59} disappearance indicates at least two dominant rate-determining

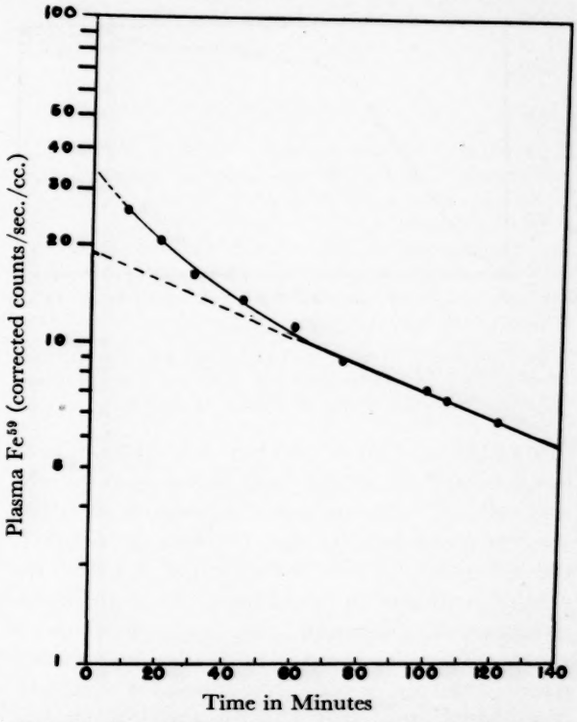

FIG. 11. Case E. F., plot on semi-log graph of rate of disappearance of plasma Fe^{59} after intravenous injection of ferric-59-β-globulinate. Broken lines indicate extrapolation of rapid and slow rate-determining components to zero time.

TABLE II
DISAPPEARANCE OF RADIOIRON BETA-1-GLOBULINATE FROM THE PLASMA

Time of Specimen (min.)	Net Counts/cc.-sec. (plasma)	Corrected Counts/cc.-sec.* (plasma)
10	25.2	25.2
20	20.4	20.4
30	16.0	16.1
45	13.7	13.7
60	11.2	11.3
75	8.9	9.0
100	7.1	7.2
106	6.7	6.8
121	5.7	5.8

* After correction for total counts per second withdrawn in preceding specimens.

factors, one causing very rapid initial disappearance, the other operating more slowly. The significance of these components is now under investigation.

The functional integrity of the bone marrow erythropoietic tissue can be judged also by the

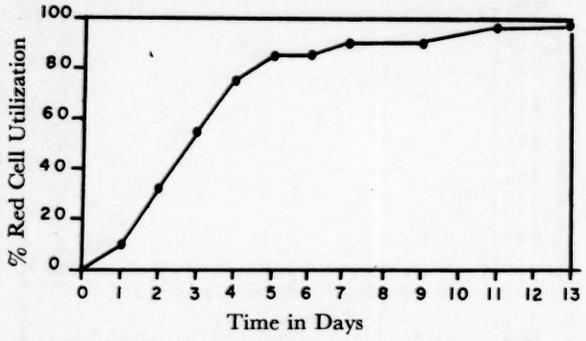

FIG. 12. Case E. F., time curve showing per cent utilization of Fe^{59} by circulating red cells after intravenous injection of ferric-59-β-globulinate at zero time.

rate of incorporation and per cent utilization of intravenously injected radioactive iron by the red cells.[13–15] Numerous variables may affect the uptake of iron by the red cells, particularly the adequacy of the body iron stores and the rate of hemoglobin breakdown. Thus in hemochromatosis, although the bone marrow is morphologically normal and anemia is infrequent, the rate of radioiron uptake is markedly diminished, probably due to the low specific activity of the iron circulating through the marrow. In hemolytic anemia the rate of incorporation of tagged iron into the red cells reaches a maximum within a few days but then levels off at a concentration much below the normal.[13,14] In polycythemia, primary or secondary, the utilization of injected radioiron by the red cells is usually maximal, reaching a peak concentration of over 80 per cent of the Fe^{59} administered in four to six days.[15,18–20]

In Case E. F., as indicated in Table III and Fig. 12, over 90 per cent of the radioiron was utilized by the seventh day following injection. Since the body iron stores were adequate in this instance, as judged by the rather high normal serum iron (168 gamma per cent), and no undue hemolysis could be demonstrated, the high concentration of radioiron in the red cells implies an increased rate of erythrogenesis.

The rates of plasma and red cell iron turnover afford another measure of the metabolic activity of the iron-containing compounds of the body.[15,17–20] The normal value for plasma iron turnover is 27 mg./day, or 0.35 mg./kg. body weight/day; that for the red cell iron turnover is 20 mg./day, or 0.26 mg./kg. body weight/day. The turnover of both the plasma iron and red cell iron is increased in polycythemia vera, as would be anticipated in view of the greater red

TABLE III

PER CENT UPTAKE BY RED CELLS OF Fe^{59} INJECTED INTRAVENOUSLY (CORRECTED FOR TOTAL COUNTS/SEC. WITHDRAWN IN THE PRECEDING SPECIMENS)

Day of Experiment	Net Counts/cc.-sec. (whole blood)	Corrected Counts/cc.-sec.	Per cent Red Cell Utilization *
1	0.94	0.94	9.5
2	3.02	3.04	30.8
3	5.30	5.34	54.2
4	7.38	7.46	75.7
5	8.32	8.45	85.6
6	8.17	8.33	84.6
7	8.72	8.92	90.6
9	8.72	8.96	90.6
11	9.23	9.51	96.5
13	9.23	9.55	97.0

* Calculated from the formula:

$$\frac{\text{counts/cc.-sec.} \times \text{total blood volume}}{\text{total counts/sec. injected} \times \text{decay}}$$

cell mass. Thus Huff et al.[15] reported an average plasma iron turnover in untreated patients with polycythemia vera of 1.8 mg./kg. body weight/day, with a variation in different cases of 0.72 to 3.7 mg. The average red cell iron turnover in these cases was 1.34 mg./kg. body weight/day, the range of variation 0.5 to 3.58 mg. From these figures it would appear that, on the average, some 2.5 per cent of the total hemoglobin is renewed each day. Similar observations have been made in polycythemia secondary to the anoxemia of high altitude.[18,19] The turnover of Fe^{59} in plasma and red cells was found to increase two- to threefold as the arterial oxygen unsaturation increased and these alterations could be directly correlated with morphologic evidence of increased bone marrow erythropoiesis.

In polycythemia secondary to congenital heart disease or pulmonary fibrosis similar results have been obtained;[20] oxygen therapy produced a marked decrease in plasma and red cell iron turnover values in the secondary polycythemias but little or no change in polycythemia vera.[20]

In Case E. F. the turnover rate of Fe^{59} was accelerated both in the plasma and in the red

cells, to 1.56 mg./kg. body weight/day and 1.52 mg./kg. body weight/day, respectively, according to the formulas of Huff et al.[15] The hemoglobin renewal/day was calculated on this basis to be 2.46 per cent of the total circulating hemoglobin. This would imply an average erythrocyte life span of only 40.5 days, considerably less than the estimate based upon the rate of incorporation of glycine-N^{15} into heme and the normal survival of red cells in polycythemia vera.[11,12] In view of the participation of Fe^{59} in many reactions not involving complete hemoglobin biosynthesis, estimates of the hemoglobin renewal rate and erythrocyte life span in polycythemia, when based upon Fe^{59} turnover rates, doubtless are subject to very large error.

SUMMARY

By simultaneous use of glycine-N^{15} and Fe^{59} as tracers the interrelationships between purine, porphyrin and iron metabolism were studied in a patient with gout associated with polycythemia secondary to congenital heart disease.

The time course of glycine-N^{15} incorporation into uric acid was unlike that previously observed in normal subjects and in patients with primary gout, in whom peak enrichment of uric acid N^{15} occurs within two to four days of administration of the isotope. In the case recorded herein there was progressive increase in the N^{15} abundance of the urinary uric acid until the tenth day. The protracted uric acid biosynthesis observed in this instance of secondary gout is presumed to reflect the augmented turnover of red cell precursor nucleic acids associated with increased erythropoiesis characterizing the polycythemic state.

The time course of glycine-N^{15} incorporation into heme in this case of secondary polycythemia did not deviate significantly from the normal, thus corresponding with the similar findings reported in polycythemia vera.

As in other recorded instances of increased erythropoietic activity due to primary and secondary polycythemia, the initial half-time of disappearance of injected Fe^{59} from the blood plasma was reduced (in this case to thirty-one minutes), the rate of Fe^{59} incorporation into circulating red cells was correspondingly accelerated and the utilization of the Fe^{59} for erythrogenesis was increased, by the seventh day, to over 90 per cent of the amount injected. The turnover rate of Fe^{59} was accelerated both in the plasma and in the red cells.

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REFERENCES

1. Buchanan, J. M. Studies on the biosynthesis of purines in vitro. In: Phosphorus Metabolism, McElroy, W. D. and Glass, B. (editors), vol. 2, p. 406. Baltimore, 1952. Johns Hopkins Press.
2. Benedict, J. D., Roche, M., Yü, T. F., Bien, E. J., Gutman, A. B. and Stetten, DeW., Jr. The incorporation of glycine nitrogen into uric acid in normal and gouty man. *Metabolism*, 1: 3, 1952.
3. Benedict, J. D., Yü, T. F., Bien, E. J., Gutman, A. B. and Stetten, DeW., Jr. A further study of the utilization of dietary glycine nitrogen for uric acid synthesis in gout. *J. Clin. Investigation*, 32: 775, 1953.
4. Muller, A. F. and Bauer, W. Uric acid production in normal and gouty subjects, determined by N^{15} labeled glycine. *Proc. Soc. Exper. Biol. & Med.*, 82: 47, 1953.
5. Gutman, A. B. Primary and secondary gout. *Ann. Int. Med.* (In press.)
6. Shemin, D. and Rittenberg, D. The biological utilization of glycine for the synthesis of the protoporphyrin of hemoglobin. *J. Biol. Chem.*, 166: 621, 1946.
7. Wittenberg, J. and Shemin, D. The location in protoporphyrin of the carbon atoms derived from the α-carbon atom of glycine. *J. Biol. Chem.*, 185: 103, 1950.
8. Muir, H. M. and Neuberger, A. The biogenesis of porphyrins. 2. The origin of the methyne carbon atoms. *Biochem. J.*, 47: 97, 1950.
9. Shemin, D. and Rittenberg, D. The utilization of glycine for the synthesis of a porphyrin. *J. Biol. Chem.*, 159: 567, 1945.
10. Shemin, D. and Rittenberg, D. On the utilization of glycine for uric acid synthesis in man. *J. Biol. Chem.*, 167: 875, 1947.
11. London, I. M., Shemin, D., West, R. and Rittenberg, D. Heme synthesis and red blood cell dynamics in normal humans and in subjects with polycythemia vera, sickle cell anemia and pernicious anemia. *J. Biol. Chem.*, 179: 463, 1949.
12. Berlin, N. I., Lawrence, J. H. and Lee, H. C. The life span of the red blood cell in chronic leukemia and polycythemia. *Science*, 114: 385, 1951.
13. Dubach, R., Moore, C. V. and Minnich, V. Studies in iron transportation and metabolism. v. Utilization of intravenously injected radioactive iron for hemoglobin synthesis, and an evaluation of the radioactive iron method for studying iron absorption. *J. Lab. & Clin. Med.*, 31: 1201, 1946.
14. Finch, C. A., Gibson, J. G., Peacock, W. C. and Fluharty, R. G. Iron metabolism: utilization of intravenous radioactive iron. *Blood*, 4: 905, 1949.

15. Huff, R. L., Hennessy, T. G., Austin, R. E., Garcia, J. F., Roberts, B. M. and Lawrence, J. H. Plasma and red cell iron turnover in normal subjects and in patients having various hematopoietic disorders. *J. Clin. Investigation*, 29: 1041, 1950.
16. Wasserman, L. R., Rashkoff, I. A., Leavitt, D., Mayer, J. and Port, S. The rate of removal of radioactive iron from the plasma—an index of erythropoiesis. *J. Clin. Investigation*, 31: 32, 1952.
17. Huff, R. L., Tobias, C. A. and Lawrence, J. H. A test for red cell production. *Acta haemat.*, 7: 129, 1952.
18. Huff, R. L., Lawrence, J. H., Siri, W. E., Wasserman, L. R. and Hennessy, T. G. Effect of changes in altitude on hematopoietic activity. *Medicine*, 30: 197, 1951.
19. Lawrence, J. H., Huff, R. L., Siri, W., Wasserman, L. R. and Hennessy, T. G. A physiological study in the Peruvian Andes. *Acta med. Scandinav.*, 142: 117, 1952.
20. Lawrence, J. H., Elmlinger, P. J. and Fulton, G. Oxygen and the control of red cell production in primary and secondary polycythemia: effects on the iron turnover patterns with Fe^{59} as tracer. *Cardiologia*, 21: 337, 1952.
21. Young, M. D. and Griswold, H. E. Situs inversus of the abdominal viscera with levocardia. *Circulation*, 3: 202, 1951.
22. Buchanan, O. H., Block, W. D. and Christman, A. A. The metabolism of the methylated purines. 1. The enzymatic determination of urinary uric acid. *J. Biol. Chem.*, 157: 181, 1945.
23. Schoenheimer, R. and Ratner, S. Studies in protein metabolism. III. Synthesis of amino acids containing isotopic nitrogen. *J. Biol. Chem.*, 127: 301, 1939.
24. Barkan, G. and Walker, B. S. Determination of serum iron and pseudo-hemoglobin iron with ortho-phenanthrolene. *J. Biol. Chem.*, 35: 37, 1950.
25. Fischer, H. In: Organic Syntheses, 21: 53, 1941.
26. Sonne, J. C., Buchanan, J. M. and Delluva, A. M. Biological precursors of uric acid carbon. *J. Biol. Chem.*, 166: 395, 1946.
27. Buchanan, J. M., Sonne, J. C. and Delluva, A. M. Biological precursors of uric acid. II. The role of lactate, glycine, and carbon dioxide as precursors of the carbon chain and nitrogen atom 7 of uric acid. *J. Biol. Chem.*, 173: 81, 1948.
28. Greenberg, G. R. De novo synthesis of hypoxanthine via inosine-5-phosphate and inosine. *J. Biol. Chem.*, 190: 611, 1951.
29. Greenberg, G. R. Conversion of 5-amino-4-imidazole carboxamide riboside to its phosphoribotide and to inosinic acid. *Federation Proc.*, 12: 211, 1953.
29*a*. Laster, L. and Muller, A. F. Uric acid production in a case of myeloid metaplasia associated with gouty arthritis, studied with glycine-N^{15}. *Am. J. Med.*, 15: 857, 1953.
30. Shemin, D. and Rittenberg, D. The life span of the human red blood cell. *J. Biol. Chem.*, 166: 627, 1946.
31. London, I. M., Shemin, D. and Rittenberg, D. Synthesis of heme in vitro by the immature non-nucleated mammalian erythrocyte. *J. Biol. Chem.*, 183: 749, 1950.
32. Callender, S. T., Powell, E. O. and Witts, L. J. The life span of the red cell in man. *J. Path. & Bact.*, 57: 129, 1945.
33. Brown, G. M., Hayward, O. C., Powell, E. O. and Witts, L. J. The destruction of transfused erythrocytes in anemia. *J. Path. & Bact.*, 56: 81, 1944.
34. Merskey, C. Red cell fragility, endogenous uric acid and red cell survival in polycythemia vera. *South African J. M. Sc.*, 14: 1, 1949.
35. Elwood, J. S. and de Wardener, H. E. The survival of transfused erythrocytes from patients with polycythaemia vera. *J. Clin. Path.*, 4: 218, 1951.
36. Watson, C. J. The Pyrrol Pigments. Handbook of Hematology. New York, 1938. Paul B. Hoeber.

Uric Acid Production in a Case of Myeloid Metaplasia Associated with Gouty Arthritis, Studied with N^{15}-Labeled Glycine*

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In recent studies of the nature of the disorder of uric acid metabolism in gout,[1–3] isotopically labeled (N^{15}) glycine was fed to normal subjects and to patients with uncomplicated gout. The subsequent abundance of N^{15} in the urinary uric acid was determined and in three gouty patients there was a normal excretion of isotope in the uric acid, while in two gouty patients there was an increased incorporation of isotope into uric acid. When excessive, the incorporation occurred at an abnormally rapid rate, reaching maximum values on the second day after ingestion of the glycine-N^{15}, and it was postulated[1] that in these patients there might be a direct pathway from glycine to uric acid which by-passed the usual source of uric acid, the nucleoproteins.

Patients with leukemia and allied disorders who develop hyperuricemia and arthritis would appear to have an increased production of uric acid due to excessive breakdown of blood cells and a rapid turnover of nucleoproteins. Such patients, when fed glycine-N^{15}, would be expected to excrete the isotope as uric acid slowly, in contrast to the gouty patients with an abnormally rapid rate of incorporation of glycine-N^{15} into uric acid.

A patient with myeloid metaplasia, hyperuricemia and arthritis was studied. The incorporation of ingested glycine-N^{15} into urinary uric acid was greater than normal but the rate of incorporation was slow, reaching a maximum value of N^{15} in urinary uric acid fifteen days after the ingestion of the glycine.

CASE REPORT§

The patient, a forty-year old white male janitor, entered the Peter Bent Brigham Hospital in 1929 with a perforated duodenal ulcer. A transection of the pylorus and a posterior gastroenterostomy were performed. The spleen was noted to be normal in appearance; the white blood cell count was 10,000 cells per cu. mm. Recovery was uneventful. On January 19, 1949, the patient, now aged sixty years and retired, entered the Massachusetts General Hospital for the first time because of superficial burns of both feet. Normal blood cell counts and a palpable, non-tender spleen were noted.

In April, 1950, following a week of intractable left upper abdominal pain, exploratory laparotomy was performed and an enlarged, adherent spleen was removed. Microscopic examination of this spleen revealed myeloid metaplasia for which no cause could be demonstrated. Mild chronic renal disease, compensated coronary artery disease and asymptomatic gallstones were also present.

Following splenectomy the patient presented

§ A portion of this case history appears in the American Practitioner and Digest of Treatment, 4: 210, 1953, as a case from the Medical Grand Rounds of the Massachusetts General Hospital.

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a host of hematologic abnormalities which persisted in varying degrees until his death, three years later. There occurred a leukocytosis ranging from 30,000 to 180,000 white blood cells per cu. mm., an unusually marked and persistent thrombocytosis and a slightly microcytic, hypochromic anemia without demonstrable associated blood loss or hemolysis. The peripheral blood contained small numbers of immature white cells and many nucleated red cells. There was poikilocytosis, anisocytosis and basophilia. The bone marrow, on repeated aspirations, was hyperplastic with a shift to the right in the myeloid elements, a shift to the left in the erythroid elements, with abundant megakaryocytes. By roentgen examination the bones had a moth-eaten, osteoporotic appearance. The liver enlarged progressively from a normal size.

Eight hospital admissions following the splenectomy were for disturbances resulting from the hematologic abnormalities. A clotting tendency caused not only three episodes of thrombophlebitis but also, in the patient's terminal months, gangrene of one foot. Multiple extensive hematomas developed as manifestations of an unexplained bleeding tendency and infection complicated the drainage of one. The anemia necessitated repeated blood transfusions and seemed to precipitate several episodes of congestive heart failure.

In September, 1950, three months after splenectomy, the serum uric acid, determined for the first time, was 6.7 gm. per cent. By December, 1951 it had risen to 7.8 gm. per cent and uric acid crystals in the urinary sediment were recorded for the first time. In July, 1952, the patient suffered his first attack of acute tenderness, stiffness, redness, swelling and severe pain in the interphalangeal joint of the left big toe, all dramatically relieved by colchicine.

In September, 1952, two days after incision and drainage of an infected hematoma and four days following an intramuscular injection of 1 cc. of mercuhydrin for mild congestive heart failure, the patient suffered a second attack of acute arthritis, now in the right big toe. On this occasion colchicine relieved the severe acute symptoms but a variable mild arthritis persisted in the right big toe for the rest of the patient's life. Three days of colchicine therapy caused diarrhea which, together with a preceding mercurial diuresis, produced a weight loss of 5 kg. Sudden total anuria followed and was relieved after eighteen hours when bilateral ureteral catheterization was performed. Uric acid gravel and stones were found in the bladder and in both ureters. A free flow of urine was immediately re-established when the ureters were cleared of the deposits. Carbonic anhydrase inhibitor was administered thereafter to produce an alkaline urine and prevent urate precipitation, and also to enhance sodium excretion.

No tophi were ever discovered. A family history of gout or other arthritis could not be elicited. Serum uric acid levels were determined for the patient's six adult offspring. Four females had levels of 4.3, 5.1, 3.6 and 5.0 mg. per cent, and two males had levels of 5.1 and 6.3 mg. per cent. The upper limit of normal for females is 5.0 and for males 6.0 mg. per cent in the laboratory in which these determinations were performed.

In order to study his uric acid metabolism the patient was admitted to the Metabolic Research Ward in November, 1952. On entry, physical examination revealed a thin, chronically ill white male weighing 52 kg., with a blood pressure of 130/70, a pulse rate of 80/minute and a respiratory rate of 16/minute. The heart was moderately enlarged with a normal sinus rhythm, frequent ventricular extrasystoles, a grade two apical systolic murmur, normal sounds and a louder aortic than pulmonic second sound. The neck veins were not distended, there was no peripheral edema, and the lungs were clear save for scattered medium inspiratory basilar rales. The abdomen was slightly tender in the epigastrium and a sharp, non-tender liver edge was palpable at the level of the right iliac crest. The interphalangeal joint of the right big toe was slightly red and tender.

The white blood cell count was 66,000 per cu. mm. with a differential count unusual only for 2 per cent normoblasts. The hemoglobin was 11 gm. per cent and the platelets were markedly increased. The alkaline urine had a specific gravity of 1.012, two plus albumin, and a few white cells, red cells, granular casts, many B. coli, and no crystals in the sediment. The guaiac test on the stool was negative. The serum contained the following: sodium 127 mEq./L., potassium 6.5 mEq./L., chloride 89 mEq./L., carbon dioxide 24 mEq./L., non-protein nitrogen 45 mg. per cent, uric acid 9.7 mg. per cent, calcium 8.1 mg. per cent, phosphorus 5.1 mg. per cent, alkaline phosphatase 13.3 Bodansky units per cent and amylase 26 units per cent.

The patient's five weeks on the ward were

marked by recurrent severe, crampy mid-abdominal pain, occasional brief bouts of explosive diarrhea, progressive arterial insufficiency to the right foot, and progressive unexplained anasarca without evidence for congestive heart failure, impaired liver function, low serum albumin or progression of his chronic renal disease. Ten days after discharge from the ward he was admitted again because of drowsiness and generalized recurrent convulsions. He died three days later on January 6, 1953.

Postmortem examination revealed severe myeloid metaplasia of the bone marrow; hematopoeisis, venous thromboses and chronic passive congestion of the liver; multiple arterial and venous thromboses involving the kidneys, left testicle, adrenals, pancreas, calf muscles, apex of the heart and the right foot; acute and subacute pancreatitis with abscess formation; bronchopneumonia and pulmonary edema; a stone in the pelvis of the left kidney; cholelithiasis; benign prostatic hypertrophy; a posterior gastroenterostomy; and swelling of the brain.

Microscopic examination of the interphalangeal joints of the great toes showed scattered small deposits of crystals giving a positive murexide test, indicating the presence of uric acid or urates in the tissues. There was an associated mild lymphocytic reaction throughout the synovial and periarticular tissues. These changes are consistent with the diagnosis of gouty arthritis.

Methods. N^{15}-labeled glycine was synthesized from potassium phthalimide using methods previously described.[3] During the study the patient was maintained on a low-protein (45 gm.), low-purine (40 mg.) diet with an average of 1,600 calories daily. His average serum uric acid level was 11.5 mg. per cent and his daily urinary excretion of uric acid was 726 ± 50 mg. During a ten-day control period the magnitude of the miscible pool of uric acid was determined[4] following the intravenous injection of 100 mg. of uric acid-1,3-N^{15}. Then he was fed labeled glycine, 100 mg. per kg. of body weight. Twenty-four-hour urine specimens were collected over a few milliliters of concentrated acetic acid, kept at 4°C., and were processed immediately. The uric acid content was determined by differential enzymatic spectrophotometry.[5] The methods employed to prepare purified uricase, to isolate uric acid from the urine, and to determine the abundance of N^{15} in the uric acid have been described elsewhere.[6–8]

The normal values, used for comparison in the diagrams, were obtained in a prior study[3] on a thirty-year old white male who weighed 82 kg., was apparently free of disease and who gave no family history of gout. His serum uric acid was 3.7 mg. per cent, and his daily urinary excretion of uric acid was 663 ± 45 mg. He was maintained on a constant 2,000 calorie diet, low in purine (140 mg.), and moderately low in protein (60 gm.). He received 100 mg. per kg. of body weight of glycine-N^{15} orally.

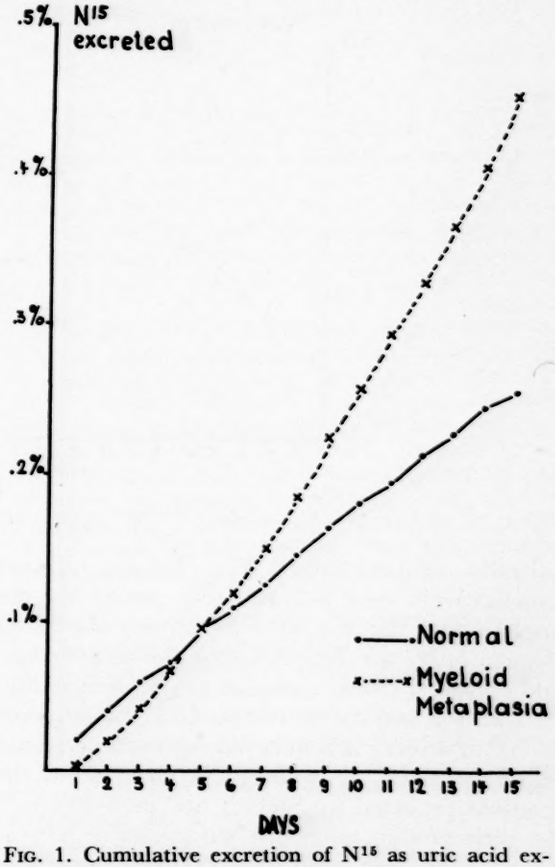

FIG. 1. Cumulative excretion of N^{15} as uric acid expressed as percentage of administered dose.

Results. The miscible pool of uric acid in the patient was determined as 2,760 mg., compared to values of approximately 1,000 mg. for normal subjects. If it is assumed that the patient's average serum uric acid level of 11.4 mg. per cent is equally distributed throughout total body water (70 per cent of body weight), a grossly approximate value of 4,150 mg. can be obtained for the patient's theoretical miscible pool of uric acid.[9] It would appear that the

larger than normal miscible pool of this patient may be ascribed entirely to the markedly elevated concentration of uric acid in his body fluids.

The daily excretion of N^{15} as uric acid was expressed as a percentage of the total dose

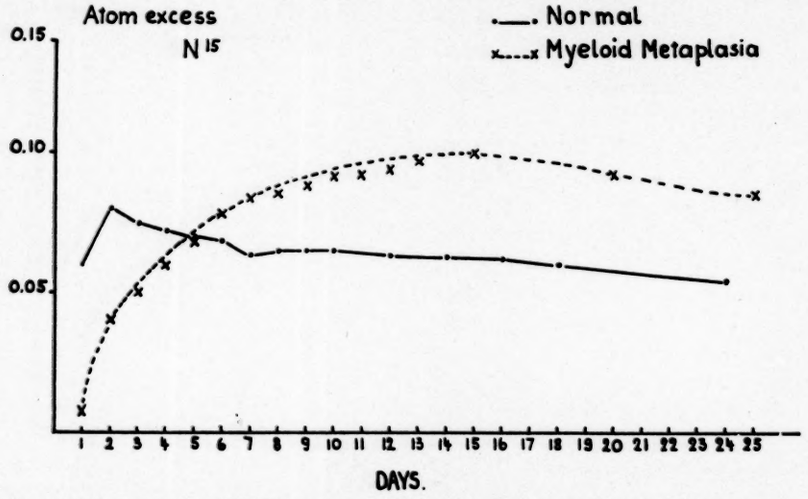

FIG. 2. Abundance of N^{15} in excreted uric acid after ingestion of tagged glycine.

initially administered. The values, plotted cumulatively over a fifteen-day period for the patient and the normal subject, are shown in Figure 1. By the fifteenth day the patient had incorporated nearly twice as much isotope into uric acid as had the normal subject. The amount of N^{15} in urinary uric acid did not exceed normal until the sixth day. This is in contrast to the findings reported by Stetten and co-workers.[1,2] In their gouty patients, when excessive N^{15} incorporation into uric acid occurred, increased excretion of N^{15} as uric acid was noted on the first day.

In Figure 2 the daily concentration of isotope in urinary uric acid is plotted for both subjects over a twenty-five-day period. The patient's curve rises slowly, does not reach a maximum value until the fifteenth day and falls off very gradually. However, curves obtained on normal subjects and on gouty patients who incorporate normal or increased amounts of N^{15} into uric acid reach maximum values by the second or third day.[1–3]

COMMENTS

The patient developed persistently elevated levels of all of the formed elements of his blood following splenectomy. Concomitantly with this presumptive increase in cellular metabolism there was a rise in the serum uric acid level, and two years after splenectomy he suffered his first attack of arthritis indistinguishable clinically from gout. It seemed reasonable to hypothesize that the hyperuricemia was caused by the increased turnover of nucleoproteins associated with the enhanced production and destruction of blood cells. If this assumption were correct, in order to appear in excreted uric acid most of a known purine precursor such as glycine would first have to enter the nucleoproteins, and the rate of its excretion would be related to the formation and destruction of the red and white blood cells. Such a concept receives support from the data presented in Figure 2 which shows a slow excretion of N^{15} as urinary uric acid. The amount of solid uric acid in the patient was limited to scattered small microscopic deposits and it is unlikely that sufficient uric acid-N^{15} could have been adsorbed by these deposits, released slowly and thereby account for the delayed excretion. The increased total amount of glycine-N^{15} incorporated into uric acid, as shown in Figure 1, might therefore be presented as evidence for the suspected increased turnover of nucleoproteins.

These results are in contrast to those reported in studies on gouty patients without hematologic abnormalities. The demonstration of a rapid excessive incorporation of glycine-N^{15} into uric acid in some gouty patients suggested to Stetten and co-workers that there might be a rapid mechanism for the transformation of dietary glycine into uric acid.[1] As they pointed out, this mechanism could involve either an unknown,

more direct pathway from glycine to uric acid, or the same intermediates which normally occur in uric acid production but with marked enhancement of the turnover rate of a portion of the nucleic acid purines. Other gouty patients (without hematologic abnormalities) did not incorporate more glycine into uric acid than did normal subjects.[2,3]

To date, then, gouty patients have been found to incorporate either normal or excessive amounts of fed glycine-N^{15} into urinary uric acid. When the incorporation was noted to be excessive the rate of transformation was rapid in the subjects without blood cell disease, and slow in the case presented here with myeloid metaplasia and the clinical picture of gout. Similar excessive but slow incorporation of glycine-N^{15} into uric acid was noted also in a case with secondary polycythemia, hyperuricemia and gout studied by Yü et al.[10]

Whether these results demonstrate the existence of distinctive, unrelated biochemical processes or different phases of a single underlying defect characteristic of the clinical entity, gout, remains to be elucidated.

SUMMARY

A patient with agnogenic myeloid metaplasia, hyperuricemia and the clinical picture of gouty arthritis was fed a single dose of glycine-N^{15} while on a diet poor in purines and proteins. The percentage of N^{15} excreted as urinary uric acid was found to be twice normal after fifteen days. The daily excretion of N^{15} in urinary uric acid increased slowly and reached a maximum value on the fifteenth day, falling off gradually thereafter. The miscible pool of uric acid was found to be 2,760 mg.

The results were interpreted as indicating that in the patient studied dietary glycine entered blood cell nucleoproteins in increased amounts and was excreted as uric acid at a rate that was related to the life span of the red and white blood cells.

Acknowledgment: We wish to thank Dr. Gordon L. Brownell, in whose laboratory the isotope analyses were carried out. Dr. Bernard M. Jacobson of the Massachusetts General Hospital, who made the hematologic observations, was kind enough to allow us to study his patient for whom he had cared since the splenectomy. We also wish to express our gratitude to Dr. Walter Bauer for his encouragement and suggestions.

REFERENCES

1. Benedict, J. D., Roche, M., Yü, T. F., Bien, E. J., Gutman, A. B. and Stetten, DeW., Jr. Incorporation of glycine nitrogen into uric acid in normal and gouty man. *Metabolism*, 1: 3, 1952.
2. Benedict, J. D., Yü, T. F., Bien, E. J., Gutman, A. B. and Stetten, DeW., Jr. A further study of the utilization of dietary glycine nitrogen for uric acid synthesis in gout. *J. Clin. Investigation*, 32: 775, 1953.
3. Muller, A. F. and Bauer, W. Uric acid production in normal and gouty subjects, determined by N^{15} labeled glycine. *Proc. Soc. Exper. Biol. & Med.*, 82: 47, 1953.
4. Benedict, J. D., Forsham, P. H. and Stetten, DeW., Jr. The metabolism of uric acid in the normal and gouty human studied with the aid of isotopic uric acid. *J. Biol. Chem.*, 181: 183, 1949.
5. Praetorius, E. An enzymatic method for the determination of uric acid by ultraviolet spectrophotometry. *Scandinav. J. Clin. & Lab. Invest.*, 1: 222, 1949.
6. Muller, A. F. and Bauer, W. A new method for preparing highly purified uricase suitable for uric acid determination by ultraviolet spectrophotometry. *J. Lab. & Clin. Med.*, 41: 497, 1953.
7. Bishop, C., Garner, W. and Talbott, J. H. Pool size, turnover rate, and rapidity of equilibration of injected isotopic uric acid in normal and pathological subjects. *J. Clin. Investigation*, 30: 879, 1951.
8. Sprinson, D. B. and Rittenberg, D. The rate of interaction of the amino acids of the diet with the tissue proteins. *J. Biol. Chem.*, 180: 715, 1949.
9. Benedict, J. D., Forsham, P. H., Roche, M., Soloway, S. and Stetten, DeW., Jr. The effect of salicylates and adrenocorticotropic hormone upon the miscible pool of uric acid in gout. *J. Clin. Investigation*, 29: 1104, 1950.
10. Yü, T. F., Wasserman, L. R., Benedict, J. D., Bien, E. J., Gutman, A. B. and Stetten, DeW., Jr. A simultaneous study of glycine-N^{15} incorporation into uric acid and heme, and of Fe^{59} utilization, in a case of gout associated with polycythemia secondary to congenital heart disease. *Am. J. Med.*, 15: 845, 1953.

Multiple Myeloma Simulating Hyperparathyroidism*

A Clinical Pathologic Study

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THE diagnosis of multiple myeloma usually suggests itself when characteristic x-ray changes in the bones are detected and the blood shows hyperproteinemia. Confirmatory evidence for the diagnosis is the demonstration of plasma cells in the bone marrow and, in most instances, Bence-Jones protein in the urine. On occasion, multiple myeloma, like most disease entities, may masquerade as something quite apart from its true identity. The case which inspired this report assumed a disguise so perfect that it eluded for a time even the close scrutiny of the pathologist. The medical history, the blood chemistry determinations and the gross and microscopic findings of a resected parathyroid tumor were consistent with the diagnosis of parathyroid adenoma. Not until a subsequent hospital admission was the true diagnosis of multiple myeloma apparent. The patient's unexpected demise from cerebral hemorrhage enabled us to study the remaining parathyroid glands and to correlate extensive metabolic and renal studies with postmortem findings.

CASE REPORT

The patient, a fifty-nine year old weaving mill foreman, was first admitted to this hospital in January, 1944, with complaints of flank pain and dysuria. The physical examination did not disclose unusual findings. Pertinent laboratory data included a persistent 2+ to 3+ albuminuria, a few red and white cells and granular casts on microscopic examination of the urine, and a non-protein nitrogen which ranged between 40 and 44 mg. per cent. The urine concentrated to 1.024. The red blood count was 4.3 million and the hemoglobin 12.5 gm. By intravenous pyelogram a calculus was demonstrated in the right renal pelvis. This was removed by pelviolithotomy. Analysis proved it to be composed of calcium and phosphate. After an uneventful postoperative course he was discharged, apparently well.

The patient was without complaint until the summer of 1948 when he began to experience symptoms of anorexia, weight loss, dysuria, frequency of urination, nocturia and constipation. A physician informed him that he had high blood pressure. He continued to work, however, until July, 1949, when he developed symptoms of nausea, vomiting and oliguria which prompted his second admission to this hospital. On admission he was dehydrated, weak and drowsy. The blood pressure was 110/80. The heart was normal in size. The rhythm was regular. A grade II systolic murmur was heard at the apex. The retinal vessels showed Grade I arteriosclerotic changes. A 2 cm. nodule was palpated in the lower pole of the right lobe of the thyroid gland. The hemoglobin was 10.2 gm. per cent, the red cell count 3.4 million, the hematocrit 28.5 per cent, the white cell count 6,700. Albuminuria was again present. On admission the blood non-protein nitrogen was 128 mg. per cent. The serum calcium was 16.2 mg. per cent, the serum phosphorus was 3.6 mg. per cent. Total serum proteins were 8.5 gm. per cent with 4.1 gm. per cent globulin. Repeated determinations of the serum proteins during the patient's hospital stay, however, were within normal limits. The serum alkaline phos-

* From the Medical and Pathological Services, Veterans Hospital, White River Junction, Vt. Published with the permission of the Chief Medical Director of the Veterans Administration. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinions or policy of the Veterans Administration.

phatase was 8 Bodansky units. The clinical course of this patient's disease and the laboratory findings suggested the diagnosis of hyperparathyroidism and further studies were made in the effort to confirm the diagnosis.

The patient was placed on a diet limiting calcium intake to less than 230 mg./twenty-four hours. After one week three daily successive urine Sulkowitch determinations were reported as 2+, 3+ and 2+, and total twenty-four-hour calcium excretions were 80.5 mg. (urinary volume 1,842 cc.), 285 mg. (urinary volume 2,115 cc.) and 120 mg. (urinary volume 1,665 cc.), respectively. This was considered a negative study. X-rays of the long bones and skull were interpreted as showing generalized demineralization but no definite osteolytic lesions. An intravenous pyelogram demonstrated neither calculi nor nephrocalcinosis. On bed rest and parenteral fluid therapy the azotemia disappeared. A PSP test on September 1st revealed 5 per cent excretion in fifteen minutes and a total two-hour excretion of only 25 per cent. A urea clearance test on September 8th was only 24.2 per cent of normal. Most observers believed that the blood chemical and renal picture was consistent with the diagnosis of hyperparathyroidism. On September 20th the right side of the neck was explored. A parathyrpid tumor measuring 3.0 by 2.5 by 1.0 cm. was excised. (Fig. 1.) This tumor was pink and yellow and weighed 12.5 gm. It was almost stony hard and cut with greatly increased resistance. It was encapsulated and the cut surface was homogenous gray-yellow. Microscopically, it was described as follows: "All sections are similar. They consist of solid sheets and alveolar arrangements of small cells with circular and oval nuclei, many containing light-staining abundant cytoplasm while others appear to have a minimum amount of cytoplasm. There are broad bands of connective tissue passing through all sections. It is highly vascularized. Both oxyphil and basophil cells are present." (Fig. 2.) The pathologic diagnosis was parathyroid adenoma.

TABLE I

BLOOD AND SPINAL FLUID CHEMISTRY DETERMINATIONS, 1949 AND 1952

	1949 July	1949 Aug.	1949 Sept.	1952 Feb.	1952 Mar.
Serum calcium, mg. %	16.2	14.2	14.9*	15.4	12.4
Serum phosphorus, mg. %	3.7	3.0	2.1*	2.3	2.5
Alkaline phosphatase, Bodansky units	....	8.0	....	4.0	4.8
Serum total protein, gm. %	8.5	7.2	6.9	10.8	8.7
Serum albumin, gm. %	4.4	....	4.1	2.3	2.9
Serum globulins, gm. %	4.1	....	2.8	8.0	5.8
Alpha globulins, gm. %	....	....	....	1.64	....
Beta globulins, gm. %	....	....	....	0.59	....
Gamma globulins, gm. %	....	....	....	5.74	....
Fibrinogen, gm. %	....	....	....	0.75	....

Values listed represent extreme abnormal for each designated period.
* Values on day of operation, September 20, 1949. On October 3, 1949, (13 days after operation) the serum calcium was 14.6 mg. per cent and the serum phosphorus 3.0 mg. per cent.

FIG. 1. Surgical specimen 1949, diagnosed as parathyroid adenoma. The linear black markings are silk sutures.

The serum calcium and phosphorus levels did not return to normal postoperatively. (Table I.) It was suspected that the patient harbored a second parathyroid adenoma and he was advised to undergo further exploratory surgery. This he refused because he felt so well but agreed to return after discharge October 3, 1949, for follow-up study at a later date. He reported to this hospital May 4, 1950. For the first time it was noted that the blood serum coagulated within a few minutes following its withdrawal from the vein. This phenomenon prevented routine chemical studies from being carried out. He was unwilling to remain in the hospital while efforts were being directed to overcome this coagulation difficulty and he was again discharged.

He continued to work and felt well until December, 1951, when he began to experience easy fatigue and anorexia. Mild polyuria and nocturia became apparent and he developed a craving for soft drinks which he consumed in liberal amounts. In early January, 1952, he

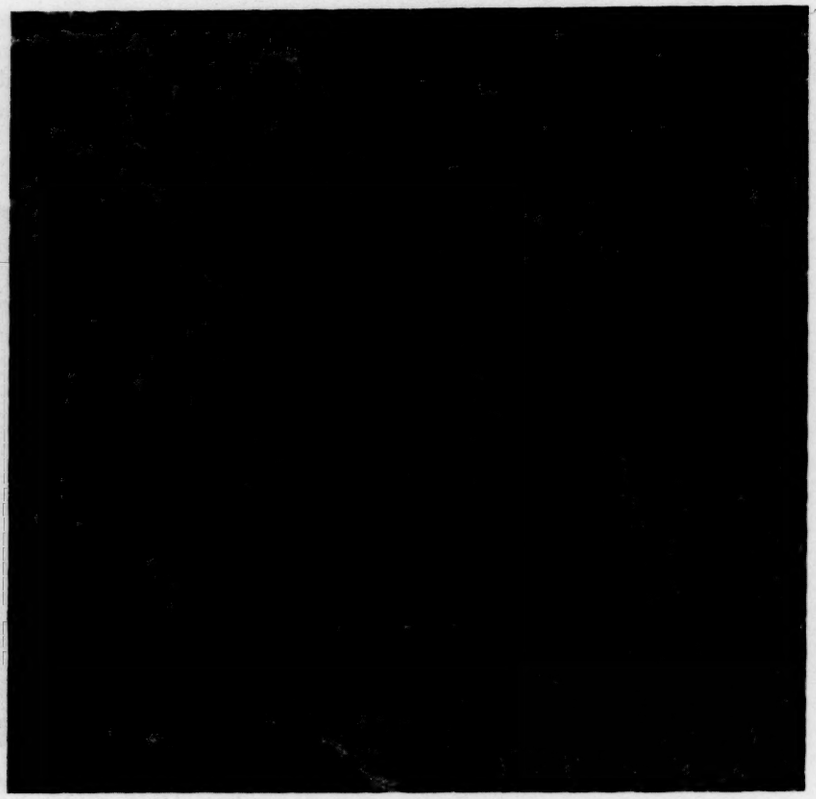

FIG. 2. Surgical specimen, originally diagnosed adenoma, showing chief cell hyperplasia; hematoxylin and eosin stain, × 1,000.

began to experience recurrent episodes of substernal indigestion-like discomfort which were usually relieved by vomiting. During seven weeks he lost approximately 18 pounds. One week before his final admission sharp excruciating pain in his lower gums began to trouble him. This pain was followed in a few minutes by severe, crushing substernal pain radiating into both arms. Such attacks were associated with profuse diaphoresis and lasted from one-half to two hours. They were not associated with exertion nor relieved by nitroglycerin. These complaints prompted his third and final admission on February 4, 1952.

The patient appeared moderately ill although he was in no distress and exhibited no signs of cardiac decompensation. There was a grayish pale hue to his face. The blood pressure was 124/78, the pulse 72, and the temperature 98.4°F. The eyes showed amorphous white deposits bordering the nasal margins of each cornea, interpreted by the ophthalmology consultant as deposits of calcium. No masses or nodules were felt in the region of the thyroid. Examination of the lungs, heart and abdomen was negative. Flexibility of the wrist and finger joints was striking. There was no purpura.

An electrocardiogram verified the clinical impression of acute myocardial infarction. The patient was immediately started on anticoagulant therapy and thereafter was maintained in good therapeutic range with 50 to 100 mg. of dicumarol daily. The initial prothrombin time was 65 per cent, a Lee-White coagulation time, eight minutes. Laboratory determinations were extremely difficult to perform because of rapid coagulability of the serum. By drawing large amounts of blood sufficient serum was obtained and the following results were reported: serum calcium 15.4 mg. per cent, serum phosphorus 2.3 mg. per cent, total protein 10.8 gm. per cent, alkaline phosphatase 4.0 Bodansky units, nonprotein nitrogen 27 mg. per cent. Fractionation of the serum proteins showed a high serum globulin with a large increase in the gamma globulin. (Table I.)

X-ray examination of the skull revealed a number of small round areas of rarefaction, one of which measured 2 cm. in diameter. This finding, in addition to hyperglobulinemia,

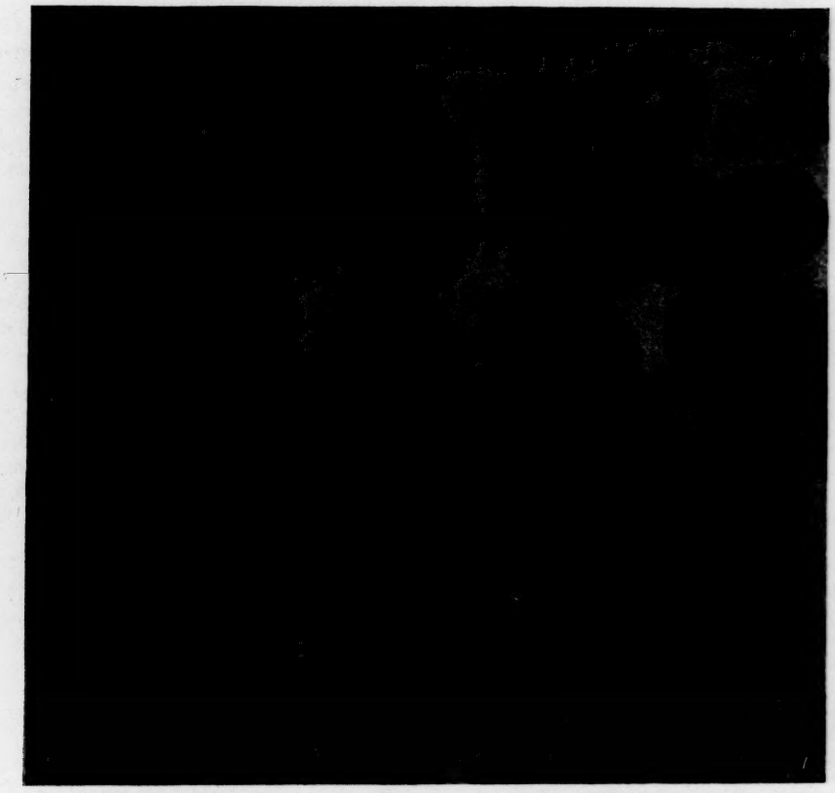

FIG. 3. Plasma cell myeloma; sternal marrow aspiration; Wright's stain, × 2,500.

raised the suspicion of multiple myeloma. The suspicion was confirmed by sternal marrow aspiration which demonstrated great numbers of plasma cells, some of which were multinucleated. (Fig. 3.) Bence-Jones protein was found intermittently in the urine. A second calcium balance study was performed. After thirty-five days on a daily calcium intake limited to 230 mg. the urinary output of calcium was 74.5 mg. (urinary volume 1,360 cc.), 63.0 mg. (urinary volume 1,520 cc.) and 41 mg. (urinary volume 1,210 cc.), respectively, for twenty-four hours. On this diet random twenty-four-hour urinalysis repeatedly showed a 2+ to 4+ Sulkowitch reaction. This study was not thought to indicate increased urinary excretion of calcium. The spinal fluid calcium was found to be 6.4 mg. per cent. The spinal fluid protein concentration at this time was 15.0 mg. per cent.

The patient maintained a good urinary output in the hospital. Renal clearance studies were done and demonstrated marked impairment. (Table II.) Serum uric acid was 8.4 mg. per cent and serum creatinine 1.5 mg. per cent. Serum cholesterol was 190 mg. per cent with 26.8 per cent free cholesterol. Serum sodium and potassium were normal. The red blood count was 3.27 million, the hemoglobin 10.7 gm. and the hematocrit 34 per cent. The blood smear showed only slight anisochromia and polychromia. Rouleaux formation of oxalated blood was not noted. The sedimentation rate remained above 100 mm./hr. (Westergren) throughout the patient's hospital stay. Withdrawal of blood through a No. 20 needle was often difficult and a No. 18 needle had to be used. Within minutes after collecting blood it was coagulated to a point where inverting the container would produce no spill. If the specimen of whole blood was then centrifuged, it would separate into three layers: a bottom layer of cells; a narrow middle layer of creamy viscid material which would gradually diffuse unevenly into a clear supernatant layer of plasma; and the latter layer which could be drawn into a separate tube but would immediately form a gel.

In an attempt to overcome this difficulty blood was collected in a warm oiled syringe and immediately placed in a 38°C. water bath from whence it was transferred to an incubator at 38°C. upon arrival in the laboratory. The following observations were recorded:

Sedimentation of red blood cells was noted to be very rapid and irregular with considerable clumping of the cells (autohemagglutination). Clotting of the plasma began in approximately one hour. At two and one-half hours there appeared to be some retraction of the plasma clot but there was little free serum. The cells which had sedimentated very rapidly before clotting began were drawn back up by the clot so that the top layer of clotted plasma became very thin. Twenty-four hours later no further clot retraction was apparent and the small amount of fluid serum noted above had become solidly clotted. The blood appeared layered as if it had been put into the tube in several portions. It was of interest that on two occasions the blood did *not* exhibit the rapid coagulation phenomenon previously mentioned. These changes could not be definitely related to any feature of his therapeutic program. Rapid coagulation could be prevented by drawing the blood into a syringe containing small amounts of sodium oxalate or heparin.

The patient was ambulated during his fourth week in the hospital. Because of satisfactory progress it was decided to maintain dicumarol therapy until he was ready for discharge. On the forty-second hospital day he complained of weakness of the right hand. A total right hemiparesis became apparent which rapidly progressed to hemiplegia. A spinal puncture demonstrated bloody spinal fluid. In spite of infusions of plasma, a transfusion of 500 cc. of blood, and large doses of vitamin K at four-hour intervals, the prothrombin time remained below 30 per cent of mean normal. Craniotomy was of no avail and the patient expired on his fifty-second hospital day.

TABLE II
RENAL FUNCTION STUDIES, 1944, 1949, 1952

	1944 Jan.	1949 July	1949 Aug.	1949 Sept.	1952 Feb.	1952 Mar.
NPN mg. %	31–44	128	71–42	36	27–41	20–29
Albuminuria	1–3+	1+	1+	1–3+	2–3+	3+
Casts/HPF	Occas.	Occas.	.....	Occas.	Occas.	Occas.
RBC's/HPF	Many	.....	.....	5–7	Occas.	Occas.
WBC's/HPF	Many	10–20	20–25	100+	Occas.	Occas.
Concentration test	1.024	.....	1.018	.....	1.026	1.021
Dilution test	.....	.....	1.010	.....	.....	.....
PSP 15 min. excretion	.....	.....	5%	5%	15%	.....
PSP 2-hr. excretion	.....	.....	65%	25%	35%	.....
Urea clearance %	.....	.....	.....	24.2	.....	.....
Inulin clearance cc./min. (*Normal values 99.3)				.....	.....	51
PAH clearance cc./min. (*Normal values 654)				.....	.....	193
Tm_{PAH} mg./min. (*Normal values 77.2)				.....	.....	32.0
C_{IN}/Tm_{PAH} (*Normal values 1.6)				.....	.....	1.59
C_{PAH}/Tm_{PAH} (*Normal values 8.44)				.....	.....	6.03
Filtration fraction (*Normal values 20.5)				.....	.....	26.4
Bence-Jones urine protein				.....	1 Neg. 1 Pos.	....
Protein excretion urine 24 hr				.....		1.65 Gm.

* Normal values taken from Smith[44] and Davies and Shock.[45]

Postmortem Findings. Postmortem examination was performed three hours after death. Pertinent findings included thrombosis of the left anterior descending coronary artery and grade III to IV sclerosis of the remaining arteries. There was evidence of recent healing infarction of the posterior third of the interventricular septum and of the adjacent portion of the left ventricle.

There was grade IV sclerosis of the cerebral arteries and there was massive hemorrhage in the right lateral ventricle and of the surrounding white matter of the cerebrum.

There were widespread changes of plasma cell myeloma. The bone marrow showed replacement by masses of plasma cells in many areas and by fibrous tissue in others. The spleen, liver and lymph nodes contained scattered foci of plasma cells within the sinusoids. There were collections of plasma cells in the interstitial

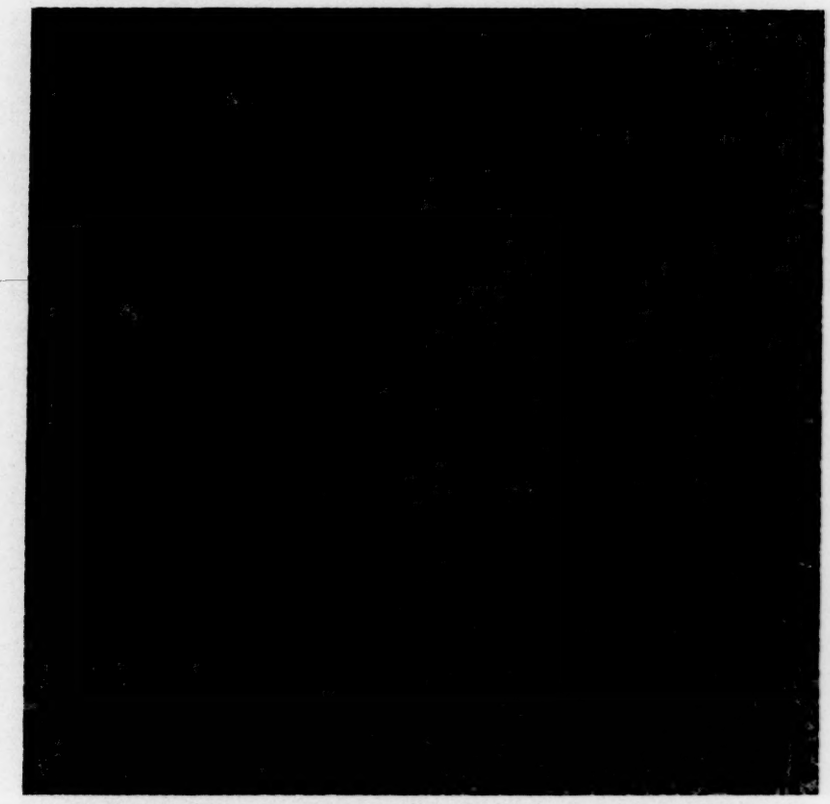

FIG. 4. Kidney; infrequent casts in tubules; hematoxylin and eosin stain, × 45.

tissue between the mucous glands of the trachea. The kidneys grossly showed little change other than that seen with a mild degree of arteriosclerosis. Microscopically (Fig. 4), scattered-collecting tubules and convoluted tubules contained eosinophilic, homogeneous casts. There were occasional tubules containing basophilic casts, surrounded in many instances by crescentic or circular syncytial masses replacing the tubular epithelium. Irregular areas of calcification were associated with some of the basophilic casts. Careful search revealed no abnormality of the glomeruli.

The thyroid gland weighed 20 gm. The left lobe was slightly larger than the right, which was bound down by dense adhesions. There were scattered 0.3 to 1.0 cm. nodules, some calcified, throughout the parenchyma. Microscopically, they showed typical changes of a nodular goiter. At the inferior pole of the left lobe were two discrete masses of tissue. (Fig. 5.) The more medial mass was firm, 1.0 cm. in greatest diameter, and weighed 2.5 gm. The surface and cut surface were pale gray brown. Lateral to this mass was a 3 by 1 cm. elongated elliptical 6.2 gm. firm mass of tissue. The outer surface was smooth and red-brown. The cut surface was gray-red and divided by fine trabeculae. No grossly normal parathyroid tissue was demonstrated in the neck or in the mediastinum. Microscopically, the masses proved to be parathyroid gland tissue. The larger gland was made up mainly of chief cells arranged in branching columns varying between 2 and 8 cells in width, the majority being under 4 cells in width. (Fig. 6.) The cells were polyhedral, had clear cell boundaries and contained granular, pale, basophilic cytoplasm and round, centrally placed nuclei with prominent chromatin dots. The average cell diameter was 7.5 micra. Many of the cells had clear cytoplasm. However, no characteristic "wasserhelle" cells were seen. There were scattered groups of oxyphil cells. No mitoses or multinucleated cells were seen and there was no striking variation in the size or shape of the cells. Adipose tissue was absent. The gland was permeated by a rich capillary network. Surrounding the gland were strands of dense fibrous tissue from which thin trabeculae extended into the gland substance,

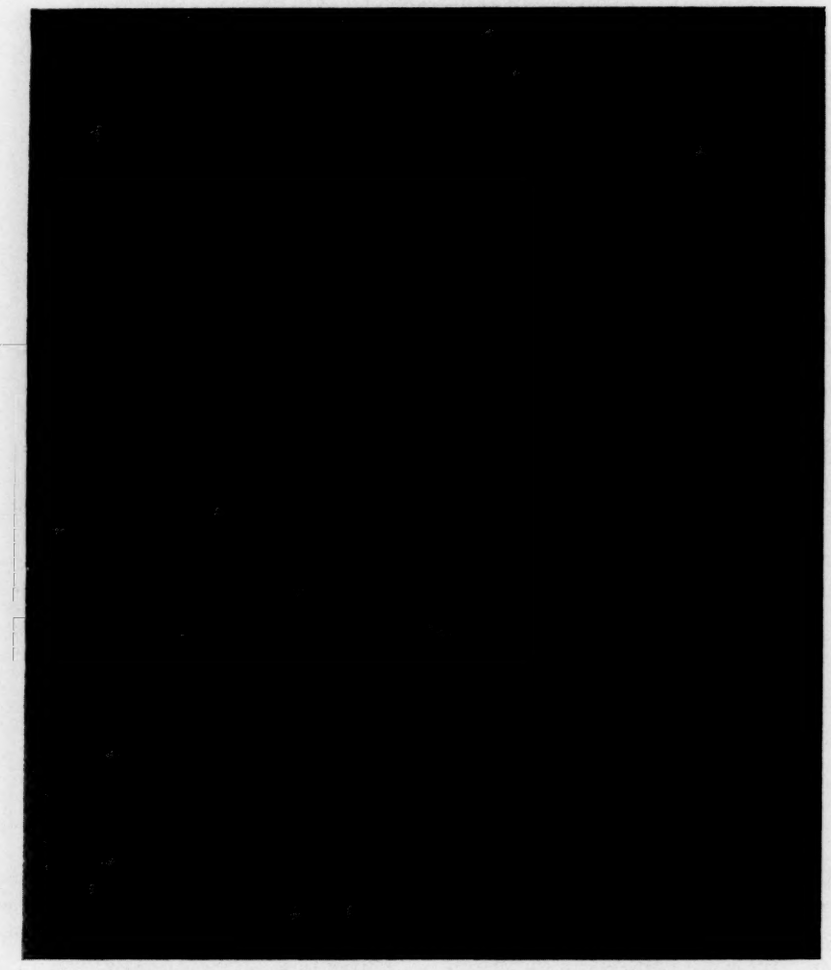

FIG. 5. Autopsy specimen, thyroid gland with attached parathyroid tissue masses; A, medial mass; B, left lateral mass.

dividing it into irregular areas. The peripheral groups of cells were compressed. Sections of the medial mass revealed an essentially similar picture with the exception that the oxyphil cell groups were more prominent. One nodule in the left lobe of the thyroid gland was made up of parathyroid gland tissue with the same structure and cell make-up as in the grossly enlarged gland tissue with the exception that oxyphil cells were not seen.

Other findings included a severe degree of bronchopneumonia bilaterally and chronic cholecystitis.

COMMENT

There are certain aspects of this case which deserve emphasis and which may be of significance in the clinical and biochemical appraisal of multiple myeloma.

Postmortem examination supplied conclusive evidence of advanced widespread multiple myeloma. The additional finding of enlarged parathyroid glands with microscopic structure similar to the parathyroid tumor removed two years previously raised several interesting diagnostic reconsiderations: (1) Was it possible that multiple parathyroid adenomas existed in this patient as a separate disease entity? (2) Might a true adenoma have been present two years previously and might the remaining parathyroid glands represent secondary hyperplasia to multiple myeloma? (3) Was multiple myeloma the underlying stimulus to secondary changes in the parathyroids in 1949 as well as in 1952?

Black and Ackerman define a parathyroid adenoma as a tumor involving one gland, usually producing hyperparathyroidism, which may recur if not completely removed and which

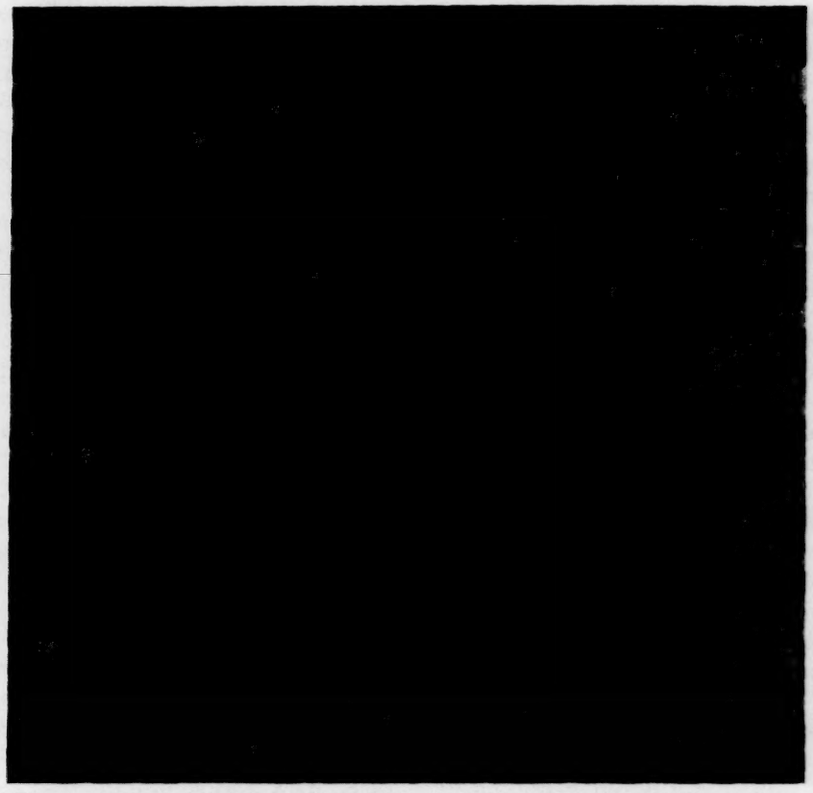

FIG. 6. Autopsy specimen; chief cell hyperplasia of parathyroid gland; hematoxylin and eosin stain, × 1,000.

does not metastasize.[1] Castleman and Mallory point out that neoplasia may be localized to one gland, part of a gland or, rarely, to parts of two glands.[2] Although cases of multiple parathyroid adenomas have been reported, a critical review of this subject by Norris concludes that there are no convincing reports of more than two adenomas occurring in the same patient.[3]

In secondary hyperplasia there is slight to moderate enlargement of all glands, but rarely, according to Castleman and Mallory, do they reach the size of the usual adenomas.[4] In some instances hyperplasia may occur at the expense of the fat content of the gland without increasing the gland size. However, Dreskin and Fox report a case wherein one hyperplastic parathyroid gland measuring 3.5 by 2.5 by 2 cm. was removed from a twenty-seven year old man with adult renal osteitis fibrosa.[5] Postoperatively there was hypocalcemia. Later, at autopsy, four nodules of parathyroid gland tissue 0.5 by 0.8 cm. showing a similar picture of secondary hyperplasia were found. The same authors cite other investigators (Gilmour and Martin, Anderson, Herbert, Magnus and Scott) who found one gland to be predominant, up to two to three times larger than others, in cases of secondary hyperplasia.

Histologically, adenomas are composed of one cell form, the commonest being chief cells. The cell arrangement can vary considerably and may be in sheets, cords, acini, papillary folds or combinations thereof. The cell size may vary as well, and multinucleated cells are common. The cells of secondary hyperplasia may also be arranged in acinar and papillary formations[7] and in some instances many of the histologic features of adenoma may be present. Differentiation of the two then becomes difficult.[3,5]

In comparing the histologic pictures of the surgically removed parathyroid gland tissue and that removed at autopsy, certain differences and resemblances were noted. The chief difference was that the predominant cell in the surgical specimen was larger than that in the autopsy specimens. However, the predominant cell in both instances was the chief cell and the arrangement of the cells was essentially similar.

There was no marked variation in the size or appearance of the cells in any of the specimens nor were mitoses or multinucleated cells seen. There was some variation in the appearance of the cytoplasm of the cells in both the surgical and autopsy specimens, and nests of oxyphil cells were seen in both. Outer limiting bands of fibrous tissue were described in all specimens and strands of penetrating fibrous tissue originating from the periphery were a feature in both.

In retrospect there is considerable clinical evidence that multiple myeloma was present in this patient at the time of surgery in 1949. The single elevated protein determination, the atypical renal disease and the postoperative hypercalcemia are strong support for this fact. The evolution of this man's illness and the microscopic similarity of the surgical and postmortem specimens of parathyroid tissue speak against primary hyperparathyroidism coexisting here with multiple myeloma. This case, we believe, illustrates the hypothesis that secondary parathyroid hyperplasia may occur in multiple myeloma[6,7] and reach tremendous proportions and that the histologic picture of secondary parathyroid hyperplasia cannot with certainty be distinguished from parathyroid adenoma.[3,5]

A second unusual feature of this case was the tendency to rapid coagulation of shed blood with poor clot retraction and failure of serum to separate from the coagulum. This abnormal coagulation of the blood was not a constant circumstance. On two occasions the blood behaved in a normal manner and laboratory determinations were carried out without difficulty. It is doubtful that this return to normality was related to dicumarol or heparin therapy which the patient received, since the coagulation abnormality recurred despite continued therapeutic effect of these drugs as judged by the prothrombin and bleeding times.

This abnormality has been infrequently commented upon in the medical literature. Wintrobe and Buell in 1933 studied a case of multiple myeloma with hyperglobulinemia in whom they observed a similar clotting tendency of shed blood. They were able to separate the abnormal serum coagulum and upon analyzing it found it to consist almost entirely of globulin.[8] In 1947 Lerner and Watson, in addition to reporting a case of their own, were able to glean from the literature a total of eight reports describing proteins which separated spontaneously from the serum. In all of these cases cooling the serum accentuated this abnormality. They therefore proposed the name cryoglobulin (cryo from the Greek word Kryos, meaning cold) as a representative name for this group of proteins.[9] The cryoglobulin of their own case was analyzed further and found to have a solubility, an ultraviolet absorption and a nitrogen content much like gamma globulin. In 1950 and 1951 Barr et al. studied three such cases in detail and found abnormal cryoglobulin fractions to have an electrophoretic pattern much like gamma globulin.[10,11]

Unfortunately, we cannot report the cryoglobulin fraction because sufficient serum could not be obtained (despite the drawing of blood in a warm oiled syringe and incubating at 38°C.) to perform this determination according to the method of Lerner and Greenberg, nor was the coagulum itself analyzed. Clotting of the plasma, however, could be prevented by adding small amounts of oxalate or heparin to the syringe, a maneuver which was unsuccessful in a case of multiple myeloma with cryoglobulinemia reported by Hill, Dunlop and Mulligan.[12] Thus it was possible to determine the other protein fractions on heparinized plasma. By the method of Kibrick and Blonstein[13] the globulin fraction was demonstrated to consist predominantly of gamma globulin. From the evidence of previously studied cases, especially that of Luckey, Russ and Barr,[10] it seems likely that the gamma fraction here also is a cryoglobulin and responsible for the hypercoagulation phenomenon described.

The course of events as observed in our patient bears out the observation of Gutman and his co-workers and others that the hypercalcemia of multiple myeloma may be independent of existing hyperproteinemia.[6,14–17] Significant is the fact that in one stage of the patient's disease the serum calcium was greater than 16 mg. per cent while the serum levels of albumin and globulin were normal. Hyperglobulinemia, which appeared later, consisted almost entirely of the gamma fraction. This fraction, according to several groups of investigators, has a low propensity to bind calcium,[15,18,19] which further suggests that the high level of calcium is on some basis other than globulin-bound calcium. The work of Rawson and Sunderman has shown that albumin as well as certain globulins may greatly increase its calcium binding capacity in multiple myeloma and may likewise contribute to hypercalcemia.[15]

Probably a logical explanation derives from the fact that myeloma is primarily a disease of bone, the breakdown of which releases a steady supply of calcium and phosphorus to the blood.[6,17,20] The impressive hyperplasia of the parathyroid glands in our own case suggests secondary hyperparathyroidism as a fourth possible explanation of abnormal calcium metabolism in this disease. The persistent tendency to hypophosphatemia in this instance is a point in favor of the latter mechanism. What might constitute the stimulus to parathyroid hyperplasia in this circumstance is obscure.[14,16] We have no evidence that hyperphosphatemia of renal origin was the responsible factor. There is on record one patient with multiple myeloma who exhibited hypophosphatemia but no alteration of parathyroid architecture at postmortem.[21]

Occasionally in the literature of multiple myeloma a reference is made to abnormal uric acid metabolism. In 1938 Stewart reported from the literature twelve patients with uric acid levels in the serum ranging from 4.1 to 31.1 mg. per cent. Nine of these listed values greater than 5 mg. per cent and seven above 6 mg. per cent. In most instances these values were not accompanied by elevated blood urea or non-protein nitrogen levels.[20] Such hyperuricemia is thought to be a reflection of nucleoprotein breakdown derived from invading tumor cells.[20] This abnormality was also apparent in the patient of this report, as evidenced by a serum uric acid level of 8.4 mg. per cent.

It is interesting that in 1949 our patient exhibited clinical evidence of severe renal insufficiency. This responded well to the usual measures and the patient thereafter was without remarkable symptoms referable to his kidneys. During his final admission in 1952 extensive renal study was done in an attempt to clarify the nature and degree of renal impairment. Marked diminution of glomerular as well as tubular function was demonstrated. Histologically, seven days later the kidneys revealed surprisingly little. Except for a few dense laminated "myeloma" casts in the distal convoluted and collecting tubules, some scattered areas of interstitial calcification and minimal evidence of nephrosis there were no changes suggesting extensive damage.

One cannot help speculating whether this patient's severe kidney dysfunction in 1949 might not have been a toxic manifestation of parathormone on the tubules, actual parathyroid poisoning,[22] or, more likely, nephrosis on the basis of widespread precipitation of protein casts in the tubules.[23–25] To be considered also is the fact that hypercalcemic states, regardless of their origin, are prone to provoke renal impairment. Calculi may form in the renal pelvis and cause a secondary pyelonephritis or there may be diffuse intra- and peritubular depositions of calcium referred to as nephrocalcinosis.[25–28] Neither was apparent by x-ray in 1949 or 1952, even though the patient's presenting complaints in 1944 were those of renal calculus. With this evidence it is unlikely that calcium deposition was the offending mechanism. The patient's unexpected death afforded us the unusual opportunity of comparing renal morphology with function. The microscopic sections demonstrated little structural alteration to account for the severe impairment of function. This feature of the "myeloma" kidney, for which there is no sound explanation, has been commented upon by others. That some process other than cast formation is responsible for this disproportion seems certain.[25,28,29] Armstrong has determined the glomerular filtration rate, the renal plasma flow and the hippurate Tm in fifteen patients with multiple myeloma. Most demonstrated significant renal impairment, some severe. He found the glomerular filtration rate in many to be depressed to a greater extent than tubular excretory capacity.[29] From these studies it is apparent that the renal damage of multiple myeloma is by no means selective. Compromise of glomerular function, blood flow and tubular excretory capacity may be severe.

Not infrequently patients with multiple myeloma succumb because of renal failure. In such instances the microscopic changes in the kidney may be striking. Dense protein casts may occlude many of the distal convoluted tubules.[23,24,26] Often the tubular cells surrounding such casts will become fused into a characteristic syncytium.[28] The proximal portions of the involved tubules may atrophy and show changes of degeneration termed "myeloma nephrosis."[28] Calcium deposition in the tubules and/or interstitium in some cases is extensive.[28] What the fundamental injury might be is still uncertain.[28,29] It is not known whether protein casts are the cause or effect of tubular degeneration.[25,29] Some suggest that the abnormal protein excreted through the kidneys is toxic to cells lining the tubules and probably to the glomeruli.[25,30,31] The work on this aspect of myeloma

is not convincing and reports such as this one offer still more uncertainty in the final analysis of the so-called "myeloma kidney."

An important clinical sign, the detection of which may lead a physician to suspect hypercalcemia, was exhibited by this patient. On the nasal and temporal margins of both corneas there was a hazy, grayish, granular film. This was determined by the slit lamp to be composed of small epithelial and subepithelial calcium deposits. These, according to Walsh and Howard,[32] run concentrically with the limbus and are usually most dense at the periphery. Clear areas within the opacity are characteristic and may help to differentiate it from band keratitis which it closely resembles.[32] The slit lamp may detect a second abnormality in the eye. This consists of small glass-like particles within the conjunctiva of the palpebral fissures. These also probably represent calcium phosphate deposits. They may cause intense irritation.[32]

Attempts have been made to find a dependable means of estimating the ionized diffusible parathyroid controlled calcium in the blood. In the early days of parathyroid study it was reasoned that the spinal fluid probably represented an ultrafiltrate of the blood and that a measure of the calcium in the spinal fluid would be a measure of the diffusible calcium in the blood.[33] This analysis, however, did not confirm expectations and it was concluded by investigators in this field that the spinal fluid calcium in hyperparathyroid states showed no significant deviation from the normal.*[34–39] As far as calcium was concerned, it did not seem that the spinal fluid was a simple dialysate in equilibrium with the blood.[20,34–37,39] In 1948 interest in the spinal fluid calcium determination was renewed when Howard and his co-workers studied the spinal fluid calcium in hypercalcemic states other than that caused by primary parathyroid disease. Curiously, the patients studied who were without apparent parathyroid disease demonstrated elevation of spinal fluid calcium approximately equal to the amount of diffusible calcium determined in the blood.[43] Explanation of this puzzling circumstance is not yet apparent. The elevated spinal fluid calcium of the case herein reported (6.4 mg. per cent) in one respect offers support to these observations. As in Howard's cases, the spinal fluid hypercalcemia was a feature of a primary disease other than hyperparathyroidism. The picture in this instance, however, is complicated by a pronounced hyperplasia of the parathyroid glands. If hyperfunction of these glands be the stimulus to hypercalcemia, it seems strange that the level of calcium in the spinal fluid should differ from that seen in parathyroid overactivity from other causes. Clarification of these problems might aid greatly in the differential diagnosis of hypercalcemia.

* The normal range of calcium in the spinal fluid (protein normal) as determined by several investigators is 4.5 to 5.5 mg./100 cc.[34,40–42]

SUMMARY

An unusual case of multiple myeloma is described which in 1949 presented the clinical picture of hyperparathyroidism. This diagnosis was substantiated by microscopic examination of an excised parathyroid tumor initially interpreted as an adenoma. The patient's hypercalcemia persisted postoperatively. Subsequent studies thirteen months later demonstrated hyperglobulinemia, radiographic changes in the skull, Bence-Jones protein in the urine and many plasma cells in the bone marrow. Extensive renal and metabolic studies were made prior to the patient's unexpected demise from cerebral hemorrhage. In addition to widespread evidence of multiple myeloma, postmortem examination revealed striking enlargement of the remaining parathyroid glands which microscopically resembled the parathyroid tumor removed in 1949. The diagnosis of primary hyperparathyroidism was discarded and multiple myeloma was considered to underlie the renal and parathyroid abnormalities exhibited by this patient.

Several interesting features of multiple myeloma are emphasized in this report: (1) Hypercalcemia is not necessarily associated with hyperproteinemia. (2) Considerable secondary hyperplasia of the parathyroid glands may occur. The differentiation between true parathyroid adenoma and secondary hyperplasia may be difficult. (3) Increased coagulability of shed blood may be encountered. This is usually related to a high level of cryoglobulins in the blood. (4) Renal clearance studies may show severe impairment of glomerular function, renal blood flow and tubular excretion of para-aminohippurate with only minimal evidence of damage microscopically. (5) The level of uric acid in the blood may be elevated. (6) Multiple myeloma, as well as hyperparathyroidism, may present with symptoms of renal calculus.

(7) Characteristic calcium deposits may occur in the eyes. (8) Calcium in the spinal fluid may be elevated.

On the basis of available evidence, we believe this case offers convincing proof that secondary hyperplasia of the parathyroid glands may be a complicating feature of the disease multiple myeloma.

REFERENCES

1. Black, B. K. and Ackerman, L. V. Tumors of the parathyroid; a review of twenty-three cases. *Cancer*, 3: 415, 1950.
2. Castleman, B. and Mallory, T. B. Pathology of the parathyroid gland in hyperparathyroidism; study of 25 cases. *Am. J. Path.*, 11: 1, 1935.
3. Norris, E. H. Collective review. The parathyroid adenoma; a study of 322 cases. *Internat. Abstr. Surg.*, 84: 1, 1947.
4. Castleman, B. and Mallory, T. B. Parathyroid hyperplasia in chronic renal insufficiency. *Am. J. Path.*, 13: 553, 1937.
5. Dreskin, E. A. and Fox, T. A. Adult renal osteitis fibrosa with metastatic calcification and hyperplasia of one parathyroid gland. *Arch. Int. Med.*, 86: 533, 1950.
6. Gutman, A. B., Tyson, T. L. and Gutman, E. B. Serum calcium, inorganic phosphorus and phosphatase activity in hyperparathyroidism, Paget's disease, multiple myeloma and neoplastic disease of the bones. *Arch. Int. Med.*, 57: 379, 1936.
7. Bulger, H. A., Dixon, H. H., Barr, D. P. and Schregardus, O. Functional pathology of hyperparathyroidism. *J. Clin. Investigation*, 9: 143, 1930.
8. Wintrobe, M. M. and Buell, M. V. Hyperproteinemia associated with multiple myeloma. *Bull. Johns Hopkins Hosp.*, 52: 156, 1933.
9. Lerner, A. B. and Watson, C. J. Studies of cryoglobulins. I. Unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitable serum globulin). *Am. J. M. Sc.*, 214: 410, 1947.
10. Luckey, E. H. Russ, E. and Barr, D. P. Cryoglobulinemia. III. Influence of a cryoglobulin on the suspension stability and sedimentation rate of erythrocytes. *J. Lab. & Clin. Med.*, 37: 253, 1951.
11. Barr, D. P., Reader, G. G. and Wheeler, C. H. Cryoglobulinemia. I. Report of two cases with discussion of clinical manifestations, incidence and significance. *Ann. Int. Med.*, 32: 6, 1950.
12. Hill, R. M., Dunlop, S. G. and Mulligan, R. M. A cryoglobulin present in high concentration in the plasma of a case of multiple myeloma. *J. Lab. & Clin. Med.*, 34: 1057, 1949.
13. Kibrick, A. C. and Blonstein, M. Fractionation of serum into albumin and alpha, beta and gamma globulin by sodium sulfate. *J. Biol. Chem.*, 176: 983, 1948.
14. Jaffe, H. L. and Bodansky, A. A. Serum calcium; clinical and biochemical considerations. *J. Mt. Sinai Hosp.*, 9: 901, 1942.
15. Rawson, A. J. and Sunderman, F. W. Studies in serum electrolytes. XV. The calcium binding property of serum proteins. (Multiple myeloma, lymphogranuloma venereum and sarcoidosis.) *J. Clin. Investigation*, 27: 82, 1948.
16. Cantarow, A. Bence-Jones proteinemia in multiple myeloma. *Am. J. M. Sc.*, 189: 425, 1935.
17. Gutman, A. B. and Gutman, E. B. Calcium protein in hyperproteinemia; total and diffusible serum calcium in lymphogranuloma inguinale and myeloma. *Proc. Soc. Exper. Biol. & Med.*, 35: 511, 1936.
18. Gutman, A. B. and Gutman, E. B. Relation of serum calcium to serum albumin and globulins. *J. Clin. Investigation*, 16: 903, 1937.
19. Drinker, N., Green, A. A. and Hastings, A. B. Equilibria between calcium and purified globulins. *J. Biol. Chem.*, 131: 641, 1939.
20. Stewart, A. and Weber, F. B. Myelomatosis. *Quart. J. Med.*, 71: 211, 1938.
21. Gill, D. Multiple myeloma simulating hyperparathyroidism. *Ann. Int. Med.*, 24: 1087, 1946.
22. Albright, F. and Reifenstein, E. C. The Parathyroid Glands and Metabolic Bone Disease, p. 77. Baltimore, 1948. Williams & Wilkins Co.
23. Blackman, S. S., Barker, W. H., Buell, M. J. and Davis, B. D. On the pathogenesis of renal failure associated with multiple myeloma. Electrophoretic and chemical analysis of protein in urine and blood serum. *J. Clin. Investigation*, 23: 163, 1944.
24. Holman, R. L. Complete anuria due to blockage of renal tubules by protein casts in a case of multiple myeloma. *Arch. Path.*, 27: 748, 1939.
25. Bell, E. T. Renal lesions associated with multiple myeloma. *Am. J. Path.*, 9: 393, 1933.
26. Albright, F., Baird, P. C., Cope, O. and Bloomberg, E. Studies on the physiology of the parathyroid glands. IV. Renal complications of hyperparathyroidism. *Am. J. M. Sc.*, 87: 49, 1934.
27. Anderson, W. H. D. Hyperparathyroidism and renal disease. *Arch. Path.*, 27: 753, 1939.
28. Allan, A. C. The Kidney, p. 277. New York, 1951. Grune & Stratton.
29. Armstrong, J. B. A study of renal function in patients with multiple myeloma. *Am. J. M. Sc.*, 219: 488, 1950.
30. Adams, W. S., Alling, E. L. and Lawrence, J. S. Multiple myeloma. Its clinical and laboratory diagnosis with emphasis on electrophoretic abnormalities. *Am. J. Med.*, 6: 141, 1949.
31. Forbus, W. D., Perlzweig, W. A. and Burwell, J. P., Jr., Effect of Bence-Jones excretion on kidneys: preliminary report. *South. M. J.*, 26: 361, 1933.
32. Walsh, F. B. and Howard, J. E. Conjunctival and corneal lesions in hypercalcemia. *J. Clin. Endocrinol.*, 7: 644, 1943.
33. Cameron, A. T. and Moorhouse, V. H. K. Tetany of parathyroid deficiency and the calcium of the blood and cerebrospinal fluid. *J. Biol. Chem.*, 63: 687, 1925.
34. Herbert, F. K. The total and diffusible calcium of the serum and the calcium of cerebrospinal fluid in human cases of hypocalcemia and hypercalcemia. *Biochem. J.*, 27: 1978, 1933.
35. Gregory, R. and Andersch, M. The filterable calcium of blood serum. I. A comparison of filterable calcium of serum and total calcium of cerebrospinal fluid in normal hyperparathyroid

and hypoparathyroid states. *Am. J. M. Sc.*, 191: 263, 1936.

36. Merritt, H. H. and Bauer, W. The equilibrium between cerebrospinal fluid and blood plasma. IV. The calcium content of serum, cerebrospinal fluid, and aqueous humor at different levels of parathyroid activity. *J. Biol. Chem.*, 90: 233, 1931.
37. Gilligan, D. R., Volk, M. C. and Altschule, M. D. The diffusibility of plasma calcium following parathormone administration. Comparison of the calcium, phosphate and protein concentrations of serum and edema fluids. *J. Biol. Chem.*, 103: 745, 1933.
38. Morgulis, S. and Perley, A. M. Studies on the cerebrospinal fluid and serum calcium with special reference to the parathyroid hormone. *J. Biol. Chem.*, 88: 169, 1930.
39. Cantarow, A. Calcium studies. VI. The effect of parathyroid extract on the diffusibility of calcium in human beings. *Arch. Int. Med.*, 44: 834, 1929.
40. Cantarow, A. and Trumper, M. Clinical Biochemistry, p. 497. Philadelphia and London, 1949. W. B. Saunders Co.
41. Stutzman, F. L. and Amatuzio, D. S. A study of serum and spinal fluid calcium and magnesium in normal humans. *Arch. Biochem. & Biophys.*, 39: 271, 1952.
42. Merritt, H. H. and Fremont-Smith, F. The Cerebrospinal Fluid, p. 12. Philadelphia, 1937. W. B. Saunders & Co.
43. Howard, J. E., Carey, R. A., Rubin, P. S. and Levine, M. D. Diagnostic problems in patients with hypercalcemia. *Tr. A. Am. Physicians*, 62: 264, 1949.
44. Berglund H., Schriver, W. de M. and Medes, G. The Kidney in Health and Disease, p. 473. Philadelphia, 1935. Lea & Febiger.
45. Davies, D. F. and Shock, N. W. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J. Clin. Investigation*, 29: 496, 1950.

Prostatic Fibrinolysin*

Study of a Case Illustrating Role in Hemorrhagic Diathesis of Cancer of the Prostate

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We have reported in previous publications[1–3] the first observations of fibrinolysis in patients with metastatic carcinoma of the prostate gland. This "prostatic fibrinolysis" presumably is caused by irruption into the blood stream of a proteolytic enzyme which is present in normal[4] and carcinomatous prostatic[2] tissue. This enzyme is responsible for the bleeding episodes which are not uncommonly observed in patients with this type of carcinoma.[1,2]

We wish to report here the case of a patient with metastatic cancer of the prostate who was observed for a period of 150 consecutive days during which repeated observations of fibrinolysis were made. A definite correlation was found between the presence of fibrinolysis and depression of the level of plasma fibrinogen as well as prolongation of the prothrombin time. Finally, this patient afforded an opportunity to study the effect of estrogenic and androgenic hormones on fibrinolysis.

MATERIAL AND METHODS

Fibrinogen was prepared by purification according to the method of Ware et al.[5] of a bovine fibrinogen preparation.‡ The fibrinogen solution was kept in the frozen state at −30°C. Before use the fibrinogen solution was thawed and kept at 37°C., and the concentration was adjusted to 0.2 per cent.

As a source of Ac globulin lyophylyzed fresh beef serum was reconstituted and adsorbed with barium carbonate according to the method of Ware et al.[6] A 1 per cent dilution in saline of this adsorbed serum was used.

Topical thrombin§ was used and diluted with saline so that 0.1 cc. represented 25 Iowa units.

Fibrinolysis was detected in the blood and the plasma of the patient by the method previously described.[1,2] Quantitative measurement of fibrinolysis in blood or in prostatic extracts was carried out by the method described by Shulman and Tagnon.[7]

Fibrinogen determinations were made on oxalated plasma by the method of Cullen and Van Slyke.[8] A modification was that clotting of the plasma was induced by the addition of 25 units of thrombin instead of by recalcification. Since fibrinolysin was present in many of the plasma samples, and in order to prevent digestion of the fibrinogen during the incubation period required by the method, an excess of soy bean trypsin inhibitor was added to every sample.[9]

The prothrombin time was determined by the one-stage method of Quick and the results were tabulated in seconds. A determination on a normal sample of human plasma was carried out every day and with every new batch of thromboplastin. Whenever a prolonged prothrombin time was discovered the determination was repeated after addition of 0.1 cc. of a 0.2 per cent fibrinogen solution and after addition of 0.1 cc. of the preparation of Ac globulin.

Prostate tissue extract was obtained by grinding the fresh human gland in M/100 phosphate buffer in saline at pH 7.4. For testing purposes an amount of this extract corresponding to 50 mg. of tissue was used. The substrate on

‡ Fraction I of Cohn, obtained from The Armour Laboratories, Chicago, Ill.

§ Preparation of Parke, Davis & Co., Detroit, Mich.

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which this prostatic extract was tested consisted of fibrinogen tagged with I-131 as described elsewhere.[7]

CASE REPORT

S. G., a fifty-eight year old Negro, was admitted on the chemotherapy service of the James Ewing Hospital on November 18, 1952, with the chief complaint of pain in the back of two years' duration. He was transferred from the Harlem Hospital to which he had been admitted in August, 1952, for the same complaint. The diagnosis made at Harlem Hospital was that of cancer of the prostate with metastases to the pelvic bones and the lumbar spine. There had been symptoms of urinary obstruction slowly progressing over the last two years prior to admission, consisting of nocturia, frequency and dribbling. Loss of libido and impotence had existed for the last two years. At the time of his admission to James Ewing Hospital the patient had not received any hormonal treatment.

Family history and past history were not contributory. In the last three years the patient had been subject to convulsive attacks diagnosed as epilepsy. He underwent herniorrhaphy in 1950. System review was entirely negative.

The patient complained mostly of a constant severe pain in the lumbar region which prevented sleep and made walking practically impossible.

The significant findings on physical examination were as follows: The patient was a well developed Negro in a satisfactory state of nutrition, lying in bed and complaining bitterly of pain in his back. The blood pressure was 127 mm. Hg systolic and 75 diastolic. Pulse was 80 and respirations were 18 per minute. Examination of the head, neck, lungs and heart did not reveal any abnormality. The abdomen had a normal appearance. There was no tenderness. Liver and spleen were not felt. No other masses were felt. The testes were small and atrophic. Rectal examination showed a prostate of normal size and normal consistency without nodules. There was marked tenderness on percussion of the low dorsal and lumbar spine. The patient could move in bed only with difficulty. There was no gynecomastia.

Roentgenologic examination revealed extensive osteoblastic metastases in the dorsal and lumbar spine, in the pelvis, femora, several ribs and humera. Roentgenologic examination of the kidneys after intravenous injection of the contrast medium failed to reveal any abnormality. The lungs and heart were normal.

The urine was free of sugar and albumin. It contained a small number of white blood corpuscles. The specific gravity fluctuated between 1.005 and 1.022. The value for hemoglobin was 7.9 gm. per 100 cc. of blood, the white blood cells amounted to 11,100 per cu. mm. of blood, with a normal differential count. The red blood cells amounted to 2,900,000 per cu. mm. of blood. The hematocrit was 24 and the sedimentation rate was 17 mm. in one hour. The reticulocyte count was 0.9 per 100 blood cells; the platelet count 255,000 per cu. mm. of blood. One or two nucleated red blood cells per 100 white cells were seen on the smear on several occasions during the course in the hospital. The eosinophil count was 81 per cu. mm. of blood. The average value of the blood urea nitrogen was 28 mg. per 100 cc. of blood and the uric acid level was 9.3 mg. The values for alkaline phosphatase and acid phosphatase were 7.7 and 13.4 glycerophosphate units, respectively. The bilirubin level was 0.38 mg. per 100 cc. of serum. The total protein level was 8.5 gm. per 100 cc. of serum of which 4.9 gm. were albumin. The bromsulphalein retention after forty-five minutes was 47 per cent. The cephalin flocculation test was 1 plus and thymol turbidity test was 3.85 Ley units.[10] Other laboratory determinations including serum electrolytes, cholesterol and cholesterol ratio, fasting blood sugar, serum inorganic phosphorus and calcium levels gave normal results. The alkaline phosphatase fluctuated between 7 and 18 units per 100 cc. of serum during the course in the hospital. The acid phosphatase level in the serum fluctuated to a considerable extent during the course as will be discussed later.

A smear of prostatic secretions obtained by prostatic massage was interpreted as containing prostatic tumor cells. A biopsy of one of the ribs demonstrated the presence of a metastatic adenocarcinoma consistent with prostatic carcinoma. A diagnosis of prostatic carcinoma with metastases in several bones was made.

Course and observations on fibrinolysis: Figures 1, 2 and 3 present the over-all laboratory data obtained during the period of observation. Figure 1 covers the period from days 1 to 44; Figure 2 from days 44 to 82 and Figure 3 from days 82 to 142. It is convenient to present the data on fibrinolysis, fibrinogen level and pro-

thrombin time in correlation with the hormonal treatment which the patient received. The first blood sample was obtained on the sixth day following admission and this corresponds to day 1 of Figure 1. Fibrinolysis was present on day 1, the fibrinogen level was 120 mg. and the day treatment by intravenous administration of diethylstilbestrol was instituted. The patient received 250 mg. daily for ten consecutive days. The treatment ended on day 14. Coincidental with this treatment fibrinolysis first became intermittent and then disappeared completely.

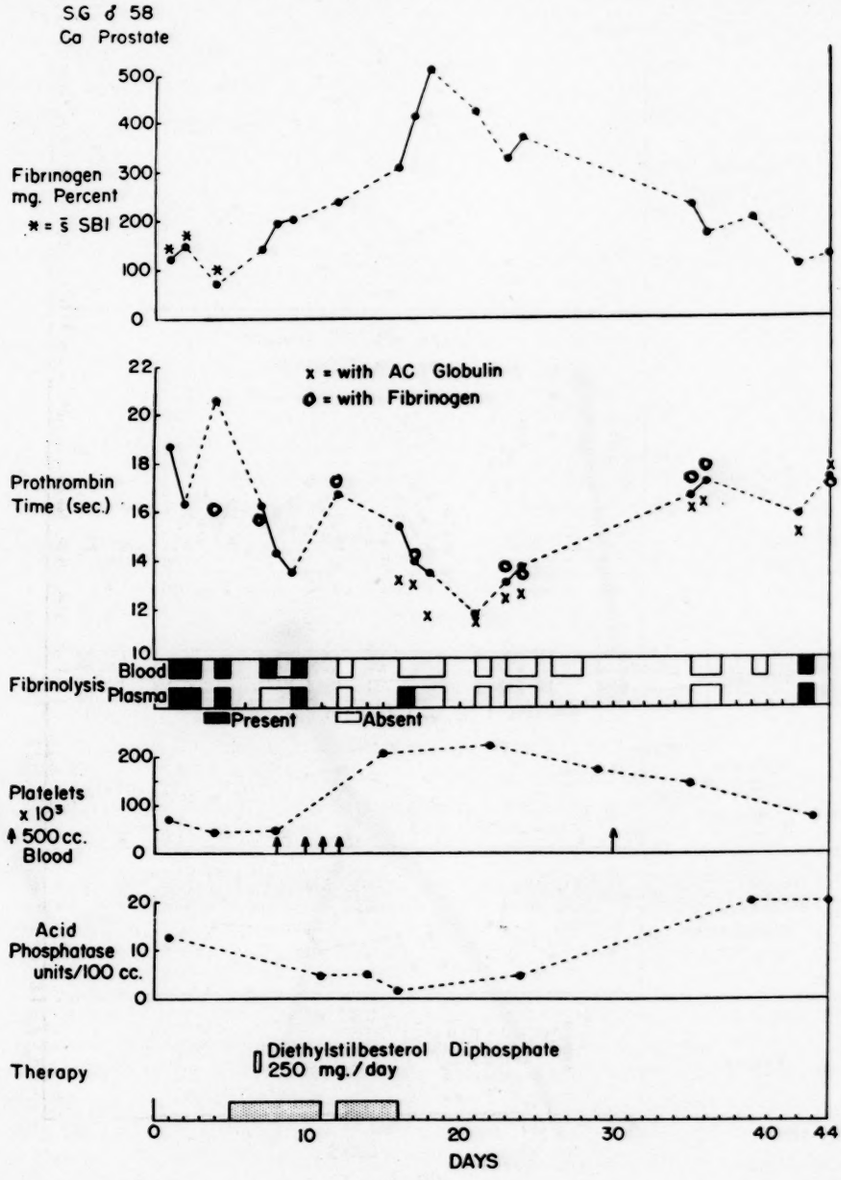

FIG. 1.

prothrombin time was nineteen seconds. There was, therefore, on day 1 a marked deficiency of fibrinogen and of the plasma prothrombin factors. On day 4 fibrinolysis was maximal and so was the deficiency of fibrinogen and the prolongation of the prothrombin time. On this

At the same time the fibrinogen level rose gradually to reach a high normal value on day 18 and the prothrombin time gradually decreased to a normal value which was reached on day 21. There was considerable improvement in the patient's pain during this period of treat-

ment. On day 18 thrombophlebitis of the left leg developed which was treated by intramuscular injections of 50 mg. of heparin given every six hours for a period of eight days. The signs of thrombophlebitis had completely disappeared four days later. Hormonal treatment was discontinued on day 14. During the period when the patient was not being treated, beginning on day 21, the fibrinogen level gradually decreased to reach a low value of 125 mg. on day 42. During the same period the prothrombin time gradually rose to reach a peak of twenty-one seconds on day 49. On day 42 fibrinolysis which had been absent reappeared, first intermittently and then constantly.

On day 51 (Fig. 2) when the fibrinogen level was low and the prothrombin time very much prolonged, treatment consisting of 0.5 mg. of ethinyl estradiol parenterally once a day was resumed. This was given for a period of twenty-five consecutive days (from days 51 to 74). During this period of treatment the fibrinogen level again rose slowly to a value of 250 mg. and the prothrombin time returned to normal.

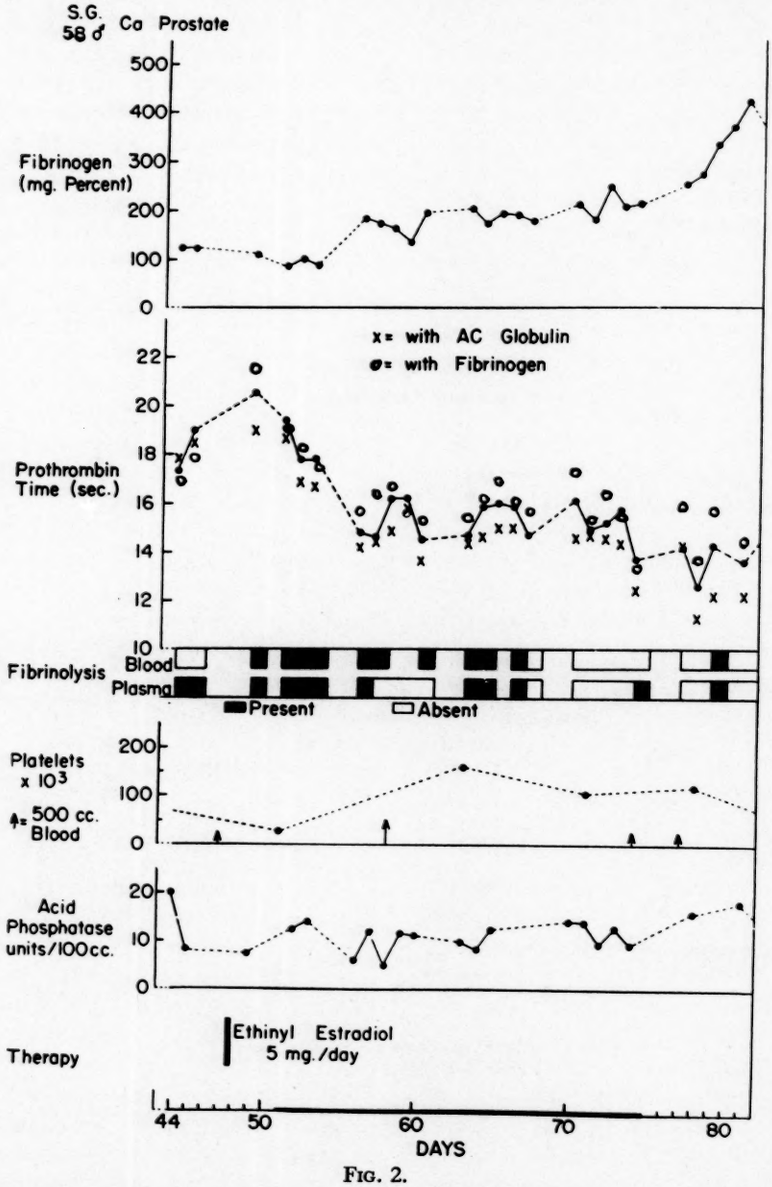

FIG. 2.

Fibrinolysis became intermittent. From days 74 to 82 no treatment was given.

From days 84 to 103 (Fig. 3), treatment with ethinyl estradiol was resumed but the daily dose was 5 mg. per day. During this period of active treatment fibrinolysis was consistently negative

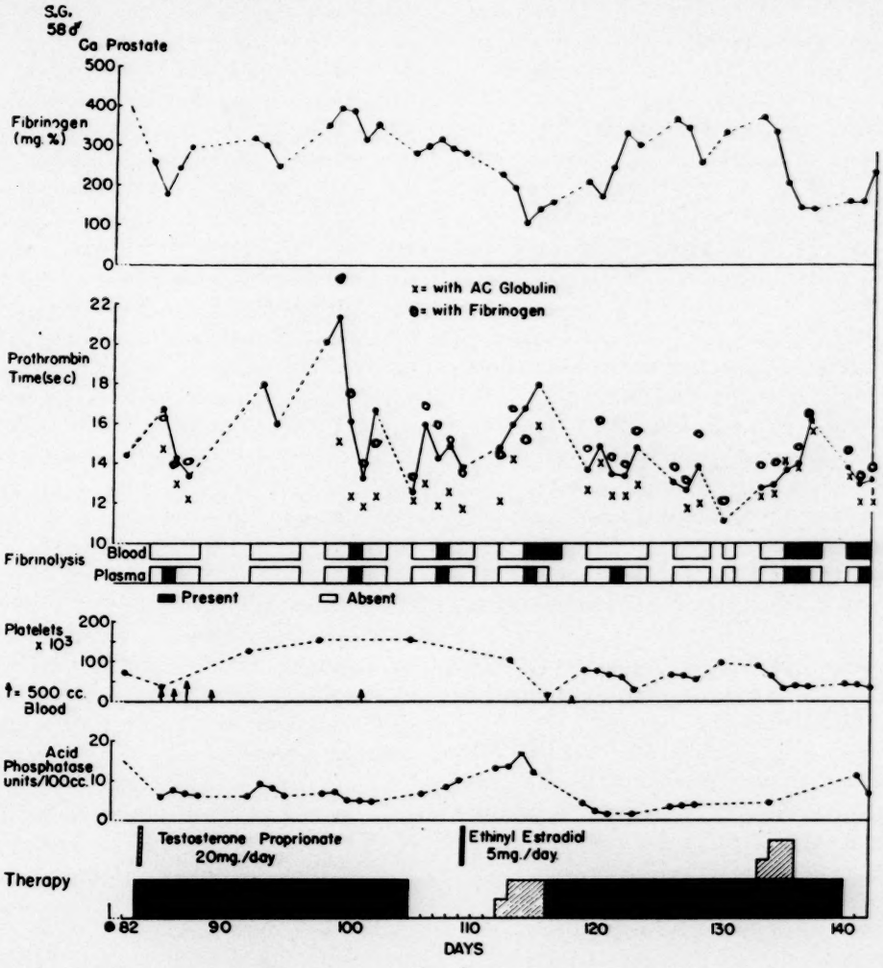

FIG. 3.

except on one occasion (day 101). The prothrombin time showed a marked prolongation on one occasion (day 98). The fibrinogen level fluctuated within the normal range.

From days 105 to 112 all treatments were discontinued in order to secure a baseline for these three values preliminary to the experimental administration of testosterone. During this period the fibrinogen level decreased somewhat although it remained within the normal range and the prothrombin time was slightly prolonged.

Administration of testosterone was begun on day 112. The patient received 10 mg. of testosterone propionate one day and 20 mg. on the three following days. This therapy was accompanied by a rapid return of the symptoms of pain and general weakness which had been relieved by the administration of the estrogenic compounds. Coincidental with the administration of testosterone, fibrinolysis reappeared. The fibrinogen level dropped to a level of 100 mg. within forty-eight hours and the prothrombin time rose from fifteen to eighteen seconds in seventy-two hours. Cessation of testosterone administration and resumption of ethinyl estradiol administration on day 116 was followed immediately by the disappearance of fibrinolysis, a gradual rise of fibrinogen level and a sharp reduction in the prothrombin time.

Administration of ethinyl estradiol was continued in doses of 5 mg. per day from days 115 to 139. However, in view of the striking effect of testosterone on the fibrinolysis, prothrombin

time and fibrinogen level observed during the preceding period, it was decided to repeat the administration of testosterone, this time without discontinuing the administration of ethinyl estradiol. Consequently, on day 134 and while estradiol was still being given, the patient received an injection of 10 mg. of testosterone propionate and of 20 mg. on the two following days. Fibrinolysis, which had been absent, reappeared immediately the day following the administration of testosterone and at the same time a sharp drop in the level of fibrinogen occurred as well as a prolongation of the prothrombin time. These values returned to normal with the disappearance of fibrinolysis as soon as the administration of testosterone was discontinued.

The patient experienced episodes of bleeding mostly in the form of epistaxis on two occasions during his course. The first time was on day 48 at a time when the fibrinogen level was depressed and the prothrombin time was prolonged; fibrinolysis was present. The second episode of epistaxis occurred with the second administration of testosterone on day 135. On both occasions the patient lost approximately 100 cc. of blood and the hemorrhage required packing of the nasal cavity.

Fluctuations in the number of platelets in the peripheral blood were roughly parallel with the fluctuation of the fibrinogen level.

As far as the acid phosphatase level in the peripheral blood is concerned, there was no consistent correlation with either the presence of fibrinolysis or the level of fibrinogen in the blood. For instance in the period extending from days 43 to 53 the fibrinogen level was very low and fibrinolysis was consistently present while the acid phosphatase level was not as high as it was during the preceding period. On the other hand, a more satisfactory correlation existed at other times; for instance on day 14 and day 122 when a low level of acid phosphatase coincided with a high level of fibrinogen and the absence of fibrinolysis.

Blood transfusions were given on different occasions as indicated on the figures and do not require special comments.

The subsequent course of the patient is not relevant to the present study.

Comment: The fibrinogen determinations recorded here were carried out with the addition of an excess of soy bean trypsin inhibitor to every sample so that these levels represent the actual amount of fibrinogen in the plasma samples before fibrinolysis *in vitro* could affect them. The prothrombin time measurements were always repeated after addition of purified fibrinogen solution to the sample of plasma and after the addition of Ac globulin; these corrected values are indicated in the figures. No soy bean trypsin inhibitor was added to the plasma used for prothrombin time determinations. A deficiency of fibrinogen in the plasma sample was responsible in one instance only for part of the prolongation of the prothrombin time. (Fig. 1, day 4.) In all other instances addition of fibrinogen did not shorten the prothrombin time and the low level of fibrinogen was therefore not responsible for prolongation of the prothrombin time. Addition of Ac globulin frequently shortened the prothrombin time significantly but did not always restore a normal value. This indicates that prolongation of the prothrombin time, when present, was due to a deficiency of Ac globulin as well as to a true deficiency of prothrombin. It is of interest to note that in the two instances in which fibrinolysis was provoked by the administration of testosterone the changes in prothrombin time and fibrinogen level preceded the appearance of fibrinolysis by one or two days and that on cessation of testosterone administration the prothrombin time returned to normal before the fibrinogen level.

To rule out the possibility that the decreased amount of fibrinogen in plasma samples showing fibrinolysis was responsible for the fibrinolysis, a quantity of purified fibrinogen corresponding to 200 mg. per 100 cc. of plasma was added to one of these samples and this addition did not prevent the appearance of fibrinolysis.

In control experiments it was shown that the addition *in vitro* of sexual hormones to the plasma of the patient did not have an inhibiting or stimulating effect of fibrinolysis.

The Effect of Prostatic Fibrinolysin on Fibrinogen and Prothrombin Time in Vitro. The occurrence of fibrinolysis simultaneously with changes in the level of plasma fibrinogen and prothrombin factors suggested that the enzyme was responsible for these changes. In order to demonstrate that the prostatic fibrinolysin can produce these changes, the following experiments were performed. An amount of extract from human prostatic carcinoma corresponding to 200 mg. of tissue was added to fresh citrated human plasma. This was incubated at 37°c. and the prothrombin time measured at intervals. In a

control experiment the same plasma was incubated with saline. Finally, a fraction of the first mixture was recalcified at the beginning of the period of incubation and the clot observed for dissolution. The results (Fig. 4) show that incubation of plasma and prostatic extract resulted in a gradual prolongation of the prothrombin time of the plasma. This prolongation could be corrected in part by the addition of Ac globulin. There was not enough digestion of fibrinogen under the conditions of the experiment to prolong the prothrombin time as shown by the fact that addition of fibrinogen did not correct the prolonged prothrombin time.

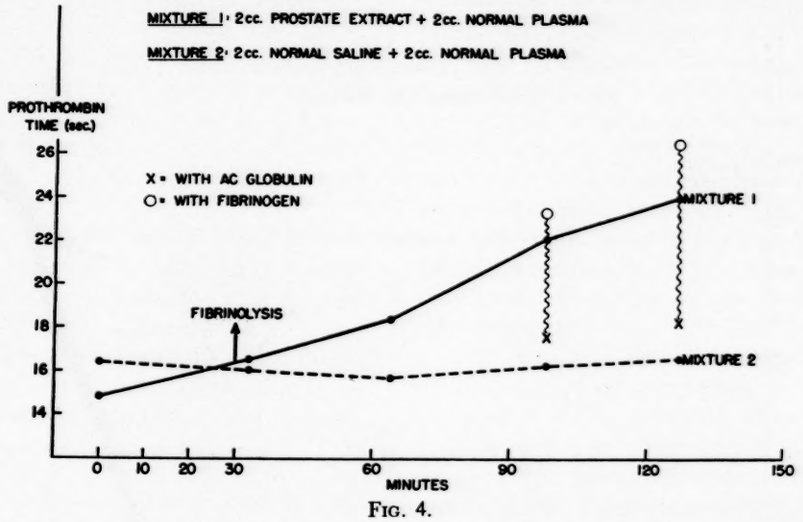

FIG. 4.

It is of interest that the plasma sample containing the clotted fibrin showed complete dissolution after incubation of one hour. This fact illustrates the greater activity of the prostatic fibrinolysin on fibrin than on fibrinogen. This greater tendency of fibrin to be digested by fibrinolysins of various origin has been reported elsewhere.

For purposes of comparison of prostatic fibrinolysin with plasmin, plasma was incubated with plasmin and similar determinations were carried out on this mixture. The results (Fig. 5) show that plasmin had essentially the same action as the prostatic fibrinolysin on the prothrombin time.

In order to ascertain that the carcinoma in the patient studied here actually contained a fibrinolysin, an extract of one of the bone metastases was prepared and tested on fibrinogen. The results indicated that this bone metastasis had definite proteolytic activity.

Effect of Testosterone Propionate on Patients with Metastatic Carcinoma of the Prostate without Fibrinolysis. The striking effect of testosterone propionate in inducing the appearance of fibrinolysis during a period of remission in the patient studied here suggested that this hormone might induce the appearance of fibrinolysis in patients with carcinoma of the prostate who do not exhibit it. Consequently four patients with cancer of the prostate and extensive bone metastases received injections of this hormone in amounts of 5 mg. one day followed by 10 mg. the following day and 20 mg. on two consecutive days. The plasma fibrinogen level and prothrombin time were measured and blood was obtained for the detection of fibrinolysis. During this short experimental period no significant change occurred in the fibrinogen level and prothrombin time, and no fibrinolysis was observable. The experiment could not be continued in these patients because of the aggravation of symptoms and signs produced by the administration of testosterone.

DISCUSSION

This patient represents another instance of the occurrence of fibrinolysis in metastatic prostatic carcinoma, the first report of which was published from this laboratory two years ago.[1] Not all patients with this disease have fibrinolysis. The incidence is approximately 12 per cent. Of patients with all types of cancers examined at all stages, only in those with metastatic carcinoma of the prostate was fibrinolysis observed.

This patient never was treated by hormones before the period of observation in this hospital. His case is of interest because he maintained an intermittent type of fibrinolysis for such a long period of time. The almost perfect correlation between the presence of fibrinolysis, the fibrinogen level and prothrombin time strongly suggests that the enzyme responsible for the fibrinolysis was also responsible for the changes in these plasma constituents. This interpretation is confirmed by the fact that prostatic fibrinolysin produces the same changes *in vitro*.

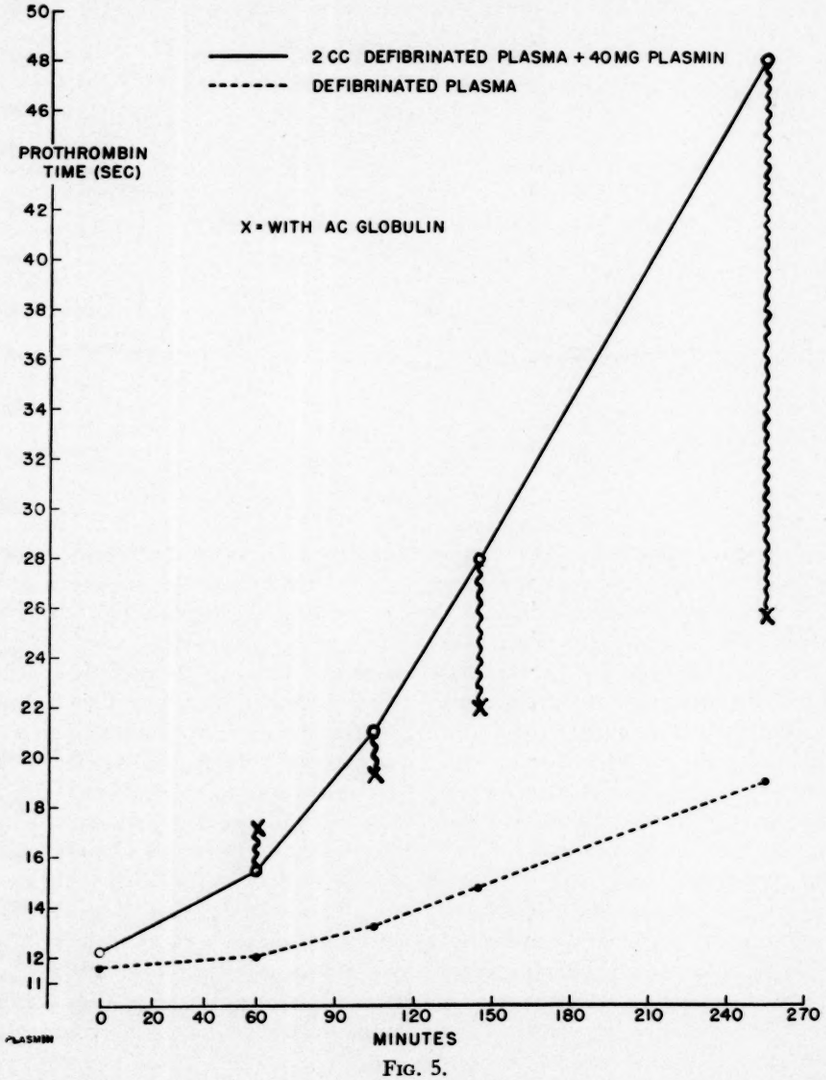

FIG. 5.

The deficiency of fibrinogen and of prothrombin factors observed in this patient was at the hemorrhagic level on several occasions. A prolongation of the prothrombin time over twenty seconds as compared to a normal value of twelve seconds, as occurred several times in our patient, may in itself produce hemorrhagic manifestations. If in addition to this prolongation of prothrombin time there is a marked deficiency of fibrinogen there seems to be little doubt that impairment of hemostasis is present. In our previous publication mention was made of the fact that hemorrhagic manifestations occurred when fibrinolysis was present.[1,2] The same observation was made in this patient. However, it should be pointed out that coincidental with the appearance of fibrinolysis, thrombocytopenia also was present in this patient. Thrombocytopenia is not an unusual manifestation of the myelophthisic type of

anemia characteristic of metastatic carcinoma of the prostate. The presence of thrombocytopenia in this patient makes it more difficult to interpret the hemorrhage as a consequence of the disturbance of the plasma clotting factors caused by the prostatic fibrinolysin. However, we have reported cases in which hemorrhagic manifestations in association with fibrinolysis occurred despite the presence of a normal level of platelets.[2] The conclusion is therefore justified that prostatic fibrinolysin can, of itself, produce a hemorrhagic diathesis characterized by fibrinogenopenia and deficiency of prothrombin and Ac globulin.

The data reported here on the effect of prostatic extract on plasma *in vitro* indicate that prostatic fibrinolysin digests fibrinogen and fibrin. Fibrin is digested at a faster rate than fibrinogen. The enzyme also digests Ac globulin and prothrombin and these effects concur to produce the prolonged prothrombin time observable in this patient. It would seem that *in vitro* the deficiency of Ac globulin is more marked than *in vivo*. However, it is possible that this difference might be due to the fact that the organism is able to replace Ac globulin faster than it is able to replace prothrombin.

No study was made of the other plasma clotting factors in relation to fibrinolysin. It is possible that these other factors, and indeed other plasma proteins not related to blood coagulation, are digested by the prostatic fibrinolysin.

The data reported here indicate that in our patient sex hormones influenced the plasma prostatic fibrinolysin to a considerable degree and indirectly influenced the level of those plasma constituents which are proteolyzed. The effect of stilbestrol during the first period of observation was very striking and so was the effect of withdrawal of stilbestrol during the following period of observation. Conversely the data show that testosterone propionate, when administered during a period in which fibrinolysin was absent and the plasma clotting factors were normal, induced the immediate appearance of fibrinolysis as well as a deficiency of fibrinogen and prolongation of the prothrombin time. This effect of testosterone propionate was elicited when given alone and could be observed when the testosterone was administered concurrently with an estrogenic hormone. Discontinuance of testosterone propionate resulted in prompt restoration of normal levels of these plasma constituents.

The opposing effects of estrogenic and androgenic hormones on prostatic fibrinolysis represent another argument in favor of the thesis that the enzyme responsible for fibrinolysis originates from the prostate gland. Two other arguments which strongly support the thesis are the demonstration of the presence of the enzyme in all samples of prostatic tissue (including metastases) tested so far[2] and also the fact that in the patient studied here the bone metastases contained a fibrinolytic enzyme which reproduced *in vitro* the changes observed in the blood of the patient. Just as the level of acid phosphatase in the blood of patients with metastatic carcinoma of the prostate is influenced by the administration of sex hormones, it would appear that in this case the fibrinolysin in the blood also was influenced by these hormones.

The fact that testosterone failed to induce fibrinolysis in four other patients with metastatic carcinoma of the prostate may be due to too short a period of administration. The hormone could not be administered for a longer time because of the deleterious effect it had on the course of the patients. Or the negative results may be explained by the fact that certain patients are resistant, at least relatively, to the effect of sex hormones. In a recent study of twenty-two patients with carcinoma of the prostate and bone metastases, only 18 per cent showed an increase in serum acid phosphatase and in symptoms on administration of testosterone propionate.[11]

Thus two enzymes are now known to be liberated into the circulating blood in patients with metastases of prostatic carcinoma. Acid phosphatase has been used for a long time as a diagnostic test and in this respect it cannot be replaced by fibrinolysis since this occurs in only approximately 12 per cent of the patients. However, the significance of acid phosphatase in the blood of the patient is purely diagnostic. So far as we know this enzyme has no function in the blood. The situation is quite different with regard to the prostatic fibrinolysin. This enzyme, when liberated into the blood stream may produce a hemorrhagic diathesis by digesting fibrinogen, Ac globulin and prothrombin.

The lack of correlation between the level of acid phosphatase and the occurrence of fibrinolysis in patients with metastatic carcinoma of the prostate is puzzling. We have data indicating that acid phosphatase is not destroyed to any great extent by prostatic fibrinolysin *in vitro*.

Therefore the lack of correlation cannot be explained on the basis of destruction of acid phosphatase *in vivo*.

In measuring plasma fibrinogen levels in patients in whom fibrinolysin is present or suspected, it is necessary to add an inhibitor to the plasma in order to prevent digestion of fibrinogen during the determination. The soy bean trypsin inhibitor is suitable for this purpose. However, its addition to plasma makes it necessary to use thrombin instead of recalcification to produce coagulation, since the inhibitor prolongs the coagulation of recalcified plasma but is not antithrombic.[9]

SUMMARY

1. The case of a patient with metastatic carcinoma of the prostate gland is reported. This patient was studied for a period of 150 days during which observations were made on blood fibrinolysis, prothrombin time and plasma fibrinogen level.

2. Fibrinolysis was present in the blood on several occasions, during which the plasma fibrinogen level decreased and the prothrombin time increased.

3. These changes could be reproduced *in vitro* by addition of extract from the prostatic cancer to plasma, indicating that the alterations in clotting factors observed in the patient were caused by the prostatic fibrinolysin released into the blood stream.

4. The prolongation of the prothrombin time was due to a deficiency of Ac globulin as well as of prothrombin.

5. Administration of estrogenic hormones brought about the disappearance of fibrinolysis and corrected the deficiency of fibrinogen and prothrombin factors. Administration of testosterone had the opposite effect.

Acknowledgment: Our thanks are due to the members of the Staff of the Chemotherapy Department for allowing us to study this patient.

REFERENCES

1. Tagnon, H. J., Whitmore, W. F. and Shulman, N. R. Fibrinolysis in metastatic cancer of the prostate. *Cancer*, 5: 9–12, 1952.
2. Tagnon, H. J., Whitmore, W. F., Schulman, P. and Kravitz, S. C. The significance of fibrinolysis occurring in patients with metastatic cancer of the prostate. *Cancer*, 6: 63–67, 1953.
3. Tagnon, H. J., Schulman, P., Whitmore, W. F. and Kravitz, S. C. The hemorrhagic syndrome of metastatic prostatic cancer and its treatment. *J. Clin. Investigation*, 31: 666, 1952.
4. Huggins, C. and Vail, V. C. Plasma coagulation and fibrinolysis by prostatic fluid and trypsin. *Am. J. Physiol.*, 139: 129–134, 1943.
5. Ware, A. G., Guest, M. M. and Seegers, W. H. Fibrinogen: with special reference to its preparation and certain properties of the product. *Arch. Biochem.*, 13: 231, 1947.
6. Ware, A. G. and Seegers, W. H. Two-stage procedure for the quantitative determination of prothrombin concentration. *Am. J. Clin. Path.*, 19: 471–482, 1949.
7. Shulman, N. R. and Tagnon, H. J. Proteolytic activity determined with a substrate tagged with radioactive iodine. *J. Biol. Chem.*, 186: 69–75, 1950.
8. Cullen, G. E. and Van Slyke, D. D. Determination of the fibrin, globulin and albumin nitrogen of blood plasma. *J. Biol. Chem.*, 41: 587, 1920.
9. Tagnon, H. J. and Soulier, J. P. Anticoagulant action of the trypsin inhibitor from soya bean flour. *Proc. Soc. Exper. Biol. & Med.*, 61: 440, 1946.
10. Ley, A. B., Lewis, J. and Davidson, C. S. The quantitative determination of the thymol turbidity reaction of serum. *J. Lab. & Clin. Med.*, 31: 910, 1946.
11. Hollander, V., West, C. D., Whitmore, W. F. and Pearson, O. H. Effect of testosterone propionate administration to patients with prostatic cancer. In press.

Hyperosmolarity of the Extracellular Fluid in Encephalitis*

With Report of a Case

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DEVIATIONS from normal of single body fluid constituents are frequently found clinically. However the maintenance of the over-all osmotic pressure of the extracellular fluid appears to be closely guarded, and deviations from normal in either direction are rare. Particularly infrequent are deviations leading to hyperosmolarity or hyperelectrolytemia because thirst is efficient in maintaining normal osmolarity by promoting the ingestion of the required amounts of water. Concurrently, the secretion of the pituitary antidiuretic hormone diminishes the loss of water by the kidneys.

During the last years a number of instances of hyperosmolarity of the extracellular fluid have been recorded,[1–10] in the majority of which the primary disturbances were disorders of the central nervous system. The following case is reported as another instance of such a disorder, presenting some features hitherto undescribed.

CASE REPORT

A fifty-one year old woman was admitted to the Rothschild Hadassah University Hospital on September 28, 1952. She had been healthy and active until about a fortnight before her admission. In March, 1952, she had been found to be slightly anemic, her blood urea at that time was 22 mg. per 100 cc. and her basal metabolic rate +13 per cent.

On September 15th she went from Tel Aviv to Jaffa in search of a relative, whose exact address she did not know, and walked about three hours in the sun. When she came home, she did not feel well and soon afterward became confused and restless, and had hallucinations. A physician who saw her at her home found a normal temperature, blood pressure of 150/100 and no other abnormal physical signs. During the next two days her psychic condition became worse and she had to be transferred to a mental institution on September 17th. At that time she was unconscious and very restless. Her temperature was 39°C. and rose two days later to 41.3°C. Her white blood count was 19.000, blood urea 77 mg. per 100 cc. During the following days her condition was essentially unchanged but she became incontinent of urine. When urine collection by catheter was instituted, the daily urinary output was found to be in the normal range. She received daily intravenous infusions of 1,000 ml. normal saline solution and 1,000 ml. of 6 per cent glucose solution, and almost every day additional amounts of fluid and nutrients, which also contained salt, were given by stomach tube. Because by that time it had become evident that she was suffering from an organic illness, she was transferred to this hospital on September 28th.

On admission to this hospital she was still deeply unconscious and restless. Her face was drawn, and skin, tongue and mucous membranes showed extreme dehydration. She was incontinent of urine and feces and was unable to swallow. Fever during the two weeks following admission was intermittent, with rises up to 39°C. in the evenings. Her pulse rate was 140 per minute but her cardiovascular system did not show other abnormalities. Neurologic examination revealed deep unconsciousness, with only very slight reaction to painful stimuli. There was divergent strabismus, the pupils reacted to light and the fundi showed no abnormalities. There was increased tonus in the right arm, normal

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TABLE I

REPRESENTING BLOOD UREA, SERUM Na, Cl, K AND CO_2, URINARY EXCRETION AND FLUID INTAKE DURING THE CRITICAL PERIOD

Date	Urea (mg.%)	Na (mEq./L.)	Cl (mEq./L.)	K (mEq./L.)	CO_2 (mEq./L.)	Urine (ml./day)	Specific Gravity	Excretion Urea (gm./day)	Excretion Na Cl (gm./day)	Tube Feeding (ml./day)	Intravenous Solutions 1/6 M Na Lact. (ml./day)	Intravenous Solutions Glucose (5–10%)*	Total Fluid Intake (ml./day)	Remarks
9/28	197				14.1	>2200					600	800	1400	
9/29	193	190	133	5.2	17.4	1200	1.007	16.3		200	600		800	
9/30	170				18.6	1000	1.008					800	800	Coma, high fever, diarrhea
10/1	172	170	130			1500				800		800	1600	
10/2	129	184	135	5.5	17.6	1500				2400			2400	
10/3	184					1800	1.008					2000		
10/4	154					1700	1.008		6.3	2400				
10/5	210					1900	1.012	20.9	7.2	2400	600	1500	4500	
10/6	122	184	121		17.5	1500	1.012	26.1	3.0	2400	600	1500	4500	Gradual return to full consciousness
10/7	175					1400	1.017	19.6	2.5	2400	600	1500	4500	
10/8	105					1850			3.3	2400	600	1500	4500	
10/9	63	137	101			1950	1.012	10.9	6.25	2400	600	1500	4500	Talks, smiles
10/10	17					2200	1.002			2400	600	1500	4500	Talks freely
10/12	14					2300	1.005	5.3	8.05					
10/18						980	1.015	3.3	3.72					
10/20	22	126	89	3.67		800	1.015							
10/27	14	147	88			650	1.002							No fever
11/6	25	137	95	4.87	29.9	1700	1.007							

* Glucose intake represents ml. / day.

tendon reflexes in both legs, a questionably positive Babinski sign. The electroencephalogram showed severe generalized disturbance of the electric activity of the brain.

Laboratory data: Sedimentation rate 165 mm. in one hour. Blood analysis: 7.5 gm. hemoglobin per 100 cc., 2,780,000 erythrocytes and 15,000 leukocytes per cu. mm., with 88 per cent polymorphonuclear cells, 2 per cent eosinophils, 8 per cent lymphocytes and 2 per cent monocytes. Urinalysis: Traces of albumin, 3–12 erythrocytes and 3–7 leukocytes per high power field. Serum chemistry: Urea 197 mg. per 100 cc., uric acid 7.4 mg. per 100 cc., glucose 118 mg. per 100 cc., sodium chloride 780 mg. per 100 cc. (calculated from 133 mEq./L. of chloride), sodium 438 mg. per 100 cc. (190 mEq./L.), potassium 20.2 mg. per 100 cc. (5.05 mEq./L.), carbon dioxide 31.5 vol. per cent (14.1 mEq./L.), total protein 6.1 gm. per 100 cc. (albumin 2.6 gm., globulin 3.5 gm.). Cerebrospinal fluid: Normal pressure, glucose 105 mg. per 100 cc., protein 12 mg. per 100 cc., the sediment contained a few white cells. Bacteria were not found; the culture was sterile.

On the basis of the history, clinical and neurologic findings and the laboratory data, diffuse encephalitis of undetermined nature, with uremia and electrolyte disturbances caused by severe dehydration, was diagnosed.

The main laboratory data during the critical period following admission are summarized in Table 1. The values for blood urea, serum sodium, chloride, potassium and carbon dioxide remained practically unchanged for about one week. During this time the patient continued to pass fairly large amounts of urine, averaging 1,600 ml. per day, with a specific gravity of 1.007 to 1.008. During most of this period she had frequent diarrhea. The daily fluid intake during the first week of hospitalization averaged about 1,200 ml. consisting mainly of 5–10 per cent glucose solution given intravenously and tube feedings. When the first high values for sodium and chloride were found, it was thought unwise to continue with the administration of sodium lactate, which had been given during the first two days. Only after a week had elapsed, and when the clinical status of the patient remained unimproved, it was decided to give her sodium lactate again in order to combat the acidosis. At the same time, tube feedings of about 2,400 ml. a day, containing mostly milk, were continued, and intravenous administration of electrolyte-free glucose solutions were given in larger amounts than before. As a consequence of this revised fluid regimen the patient received during the following six days a total of 4,500 ml. daily, as against a urinary output of 1,800 ml. daily on the average.

Almost immediately after the start of this new fluid regimen the patient began to awake from her state of coma and returned within a few days to full consciousness. She began to talk freely, but somewhat hesitatingly, and complained for a few more days of headache. During this time she slept the greater part of the day but could easily be aroused. Temperature became normal after four weeks of hospitalization, and all clinical and laboratory findings of her severe condition cleared up entirely during this period; the electroencephalogram, which was repeated on two occasions, became normal. The patient left the hospital fifty days after admission. She was admitted one month later for a check-up at which time no clinical or laboratory abnormalities were found. The renal concentration power was normal at that time.

COMMENTS

The main features of this patient's illness can be summarized as a febrile disease with acute onset, leading after a few days to deep coma. During the period of unconsciousness, dehydration, acidosis and azotemia developed, caused by a relatively large urinary flow. At the same time hyperelectrolytemia of the blood plasma with respect to sodium and chloride developed. The increase in blood sodium and chloride led to an osmotic concentration of about 400 milliosmols per L., as compared with a normal of about 310 milliosmols per L. This state of azotemia with hyperosmolarity, together with a urinary output of 1,600 ml. daily, continued unabated until the fluid intake was raised, and made to exceed the total fluid loss by about 2,000 ml. daily. The response to this fluid regimen was a reversal of the state of azotemia and hyperosmolarity of the extracellular fluid to normal, accompanied by a dramatic change for the better in the general state of the patient.

The immediate cause of the development of hypertonicity of the body fluids was obviously the continued secretion of fairly large amounts of urine with low solute content. The previous history of the patient as well as the follow-up studies did not reveal any organic basis for

impairment of the renal concentrating power. Accordingly, the explanation is probably a disturbance of the regulatory mechanism, which usually reduces the flow of urine and increases its solute content whenever the concentration of the extracellular fluid tends to rise. This regulation is accomplished in normal animals and in man by increased reabsorption of water in the distal part of the renal tubules, under the influence of the antidiuretic hormone. The mechanism governing the secretion of the antidiuretic hormone consists of the supraoptic nuclei of the hypothalamus and the adjacent region, their nervous connection with the posterior part of the pituitary gland, and the gland itself. As is likely from the work of Verney[11] the first link in the chain leading to antidiuresis are certain structures located in the supraoptic region, the so-called "osmoreceptors," which are extremely sensitive to slight changes in the osmotic concentration of the extracellular fluid. The best known disorder of this regulatory mechanism is diabetes insipidus, usually caused by damage to the posterior part of the pituitary gland. In this patient the temporary character of the disturbance seems to exclude the probability of a primary lesion in the posterior hypophysis or of an interruption of the pathways leading from the nerve centers to the gland. Moreover, the daily excretion of 1,600 to 1,800 ml. of urine of a specific gravity of 1.008–1.012 is hardly compatible with a diagnosis of diabetes insipidus. It seems more likely that the observed disorder was caused by a disturbance of the nervous center of the osmotic regulatory mechanism, the "osmoreceptors." This disturbance did not lead to complete cessation of the function of the osmotic regulatory mechanism but rather to its functioning at a higher setting of the "osmostat," resulting in a remarkably constant high osmotic level of around 400 milliosmols per L. for a period of about eight days. In this connection it may be mentioned that the return to normal in the function of the osmotic regulatory mechanism was marked by fluctuations in the sodium and chloride plasma levels, leading at one time to hypotonicity, with 126 mEq./L. of sodium and 89 mEq./L. of chloride.

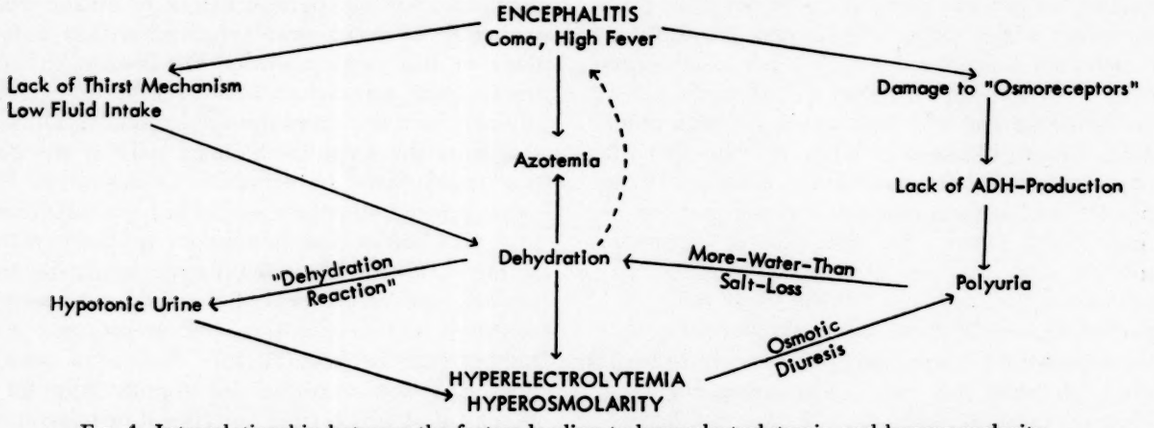

FIG. 1. Interrelationship between the factors leading to hyperelectrolytemia and hyperosmolarity.

Once the hyperosmolarity of the extracellular fluid had been established, additional mechanisms may have contributed to the continued secretion of fairly large amounts of urine, in the face of the severe state of dehydration. As the glomerular filtrate must obviously have been concentrated to a similar degree as the extracellular fluid with regard to urea and salts, a mechanism leading to "osmotic diuresis"[12] might have become active, which also leads to the excretion of copious urine with a concentration below the maximal concentrating capacity of the renal tubules.

Another factor which in our case may have contributed to the accumulation of salt in the body fluids can be found in the "dehydration reaction" described by Peters.[13] This mechanism becomes active when the volume of the extracellular fluid shrinks, and leads to increased reabsorption of salt by the renal tubules. As a consequence of this increased salt retention, water is transferred from the cells into the extracellular space in an attempt to establish osmotic equilibrium between the two compartments. At

the same time, the retained salt leads, in the presence of a normally functioning osmoregulatory mechanism, to increased tubular reabsorption of water; the latter part of the "dehydration reaction," however, did not become effective in our case because of the faulty functioning of the osmoregulatory apparatus.

Figure 1 is an attempt to depict visually the interrelationship between the various factors which led to the osmotic disturbance of the body fluids in this case. As indicated by the broken arrow, leading from "dehydration" to "coma, high fever," a vicious circle between these conditions has to be considered. This assumption, based on theoretic grounds, seems to be justified in our case by the fact that correction of the hypertonicity by rehydration had an immediate and dramatic effect on the whole picture and led to rapid recovery from the state of deep coma to full consciousness within a few days.

A comparison with other cases of hyperelectrolytemia described in the literature shows many features similar to those of our case, while in some respects divergent elements must be pointed out. Homer Smith[14] mentions reported cases of clinical disturbances of unidentified etiology with abnormal retention of sodium and chloride, "presumably of renal origin." However, these early (1939) cases of Allott[1] to which Smith refers were all associated with cerebral lesions and free from renal involvement. It is of interest to quote here an editorial in the *Lancet:* "In the cases described by Allott, for example, the various central nervous lesions found may have disturbed in some way the secretion of a pituitary hormone, and have thus led indirectly to the abnormal electrolyte metabolism."[15]

Most of the subsequently reported cases of hyperelectrolytemia and hyperosmolarity[2–10] were also connected with organic disturbances of the brain, and most of them were found in traumatic or surgical cases. In the series of Luetscher and Blackman[2] the cerebral lesions occurred together with organic renal damage caused by sulfa drugs, and in some instances together with jaundice; therefore the etiology of the observed high sodium and chloride levels in the serum is uncertain. In the majority of the published cases of hyperosmolarity, organic lesions of the brain were demonstrated at autopsy, most of them involving the frontal lobes and the hypothalamus. A search of the literature has not revealed instances of hyperosmolarity in which the cerebral disease was, as in our case, of diffuse and infectious or toxic nature. The reversibility of such cerebral disorders and the great importance of correcting the accompanying osmotic disturbance, makes it incumbent to look for hyperosmolarity in cases of coma of central origin even though the urinary volume is apparently normal.

SUMMARY

A case is reported of encephalitis of undetermined etiology which led to severe hyperelectrolytemia and hyperosmolarity of the extracellular fluid. The causes of this condition were a primary disturbance of the central osmoregulatory mechanism, a lack of antidiuretic hormone secretion and a prolonged diuresis of relatively dilute urine. Therapy consisted of rehydration by fluids low in electrolytes.

Acknowledgments: I wish to express my thanks to Dr. H. Z. Winnik for his information concerning the patient's stay at the Mental Hospital, Talbieh, and to Professor L. Halpern for repeated neurologic examinations.

REFERENCES

1. Allott, E. N. Sodium and chlorine retention without renal disease. *Lancet*, 1: 1035, 1939.
2. Luetscher, J. A., Jr. and Blackman, S. S., Jr. Severe injury to kidneys and brain following sulfathiazole administration: high serum sodium and chloride levels and persistent cerebral damage. *Ann. Int. Med.*, 18: 741, 1943.
3. Rapaport, S. Hyperosmolarity and hyperelectrolytemia in pathologic conditions of childhood. *Am. J. Dis. Child.*, 74: 682, 1947.
4. Sweet, W. H., Cotzias, G. C., Seed, J. and Yakovlev, P. I. Gastro-intestinal hemorrhages, hyperglycemia, azotemia, hyperchloremia and hypernatremia following lesions of frontal lobe in man. *A. Research Nerv. & Ment. Dis. Proc.*, 27: 795, 1948.
5. Peters, J. P. The role of sodium in the production of edema. *New England J. Med.*, 229: 353, 1948.
6. Higgins, G., Lewin, W., O'Brien, J. R. P. and Taylor, W. H. Metabolic disorders in head injury. Hyperchloraemia and hypochloruria. *Lancet*, 1: 1295, 1951.
7. MacCarty, C. S. and Cooper, I. S. Neurologic and metabolic effects of bilateral ligation of the anterior cerebral arteries in man. *Proc. Staff Meet., Mayo Clin.*, 26: 185, 1951.
8. Cooper, I. S. and MacCarty, C. S. Unusual electrolyte abnormalities associated with cerebral lesions. *Proc. Staff Meet., Mayo Clin.*, 26: 354, 1951.
9. Cooper, I. S. and Crevier, P. H. Neurogenic hypernatremia and hyperchloremia. *J. Clin. Endocrinol. & Metabol.*, 12: 821, 1952.

10. Welt, L. G., Seldin, D. W., Nelson, W. P., German, W. J. and Peters, J. P. Role of the central nervous system in metabolism of electrolytes and water. *Arch. Int. Med.*, 90: 355, 1952.
11. Verney, E. B. Antidiuretic hormone and the factors which determine its release. *Proc. Roy. Soc., London, s.B.*, 135: 25, 1947.
12. Smith, H. W. The Kidney. Structure and Function in Health and Disease, p. 613. New York, 1951. Oxford University Press,
13. Peters, J. P. Sodium, water and edema. *J. Mount Sinai Hosp.*, 17: 159, 1950.
14. Smith, H. W. The Kidney. Structure and Function in Health and Disease, pp. 372–373. New York, 1951. Oxford University Press.
15. Annotations. *Lancet*, 1: 1054, 1939.

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Abnormal Motility as the Cause of Ulcer Pain

Until recently the general opinion was held that ulcer pain was primarily caused by the presence of hydrochloric acid on the surface of the ulcer.

Present investigations[1,2] on the relationship of acidity and muscular activity to ulcer pain have led to the following concept of its etiologic factor:

> "... abnormal motility[2] is the fundamental mechanism through which ulcer pain is produced. For the production and perception of ulcer pain there must be, one, a stimulus, HCl or others less well understood; two, an intact motor nerve supply to the stomach and duodenum; three, altered gastro-duodenal motility; and four, an intact sensory pathway to the cerebral cortex."

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1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, to be published.

2. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

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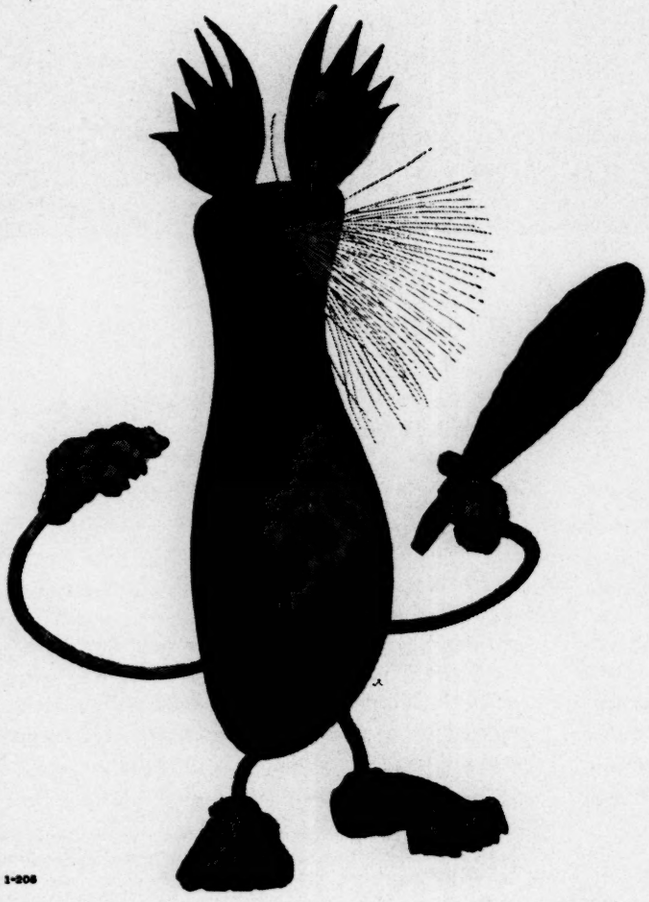

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against staphylococci—because of the high incidence of staphylococci resistant to other antibiotics.

A DRUG OF CHOICE
because it does not materially alter normal intestinal flora; gastrointestinal disturbances rare; no serious side effects reported.

ADVANTAGEOUS
because the special acid-resistant coating developed by Abbott, and Abbott's built-in disintegrator, assure rapid dispersal and absorption in the upper intestinal tract.

USE ERYTHROCIN
in pharyngitis, tonsillitis, scarlet fever, pneumonia, erysipelas, osteomyelitis, pyoderma and other indicated conditions.

Abbott

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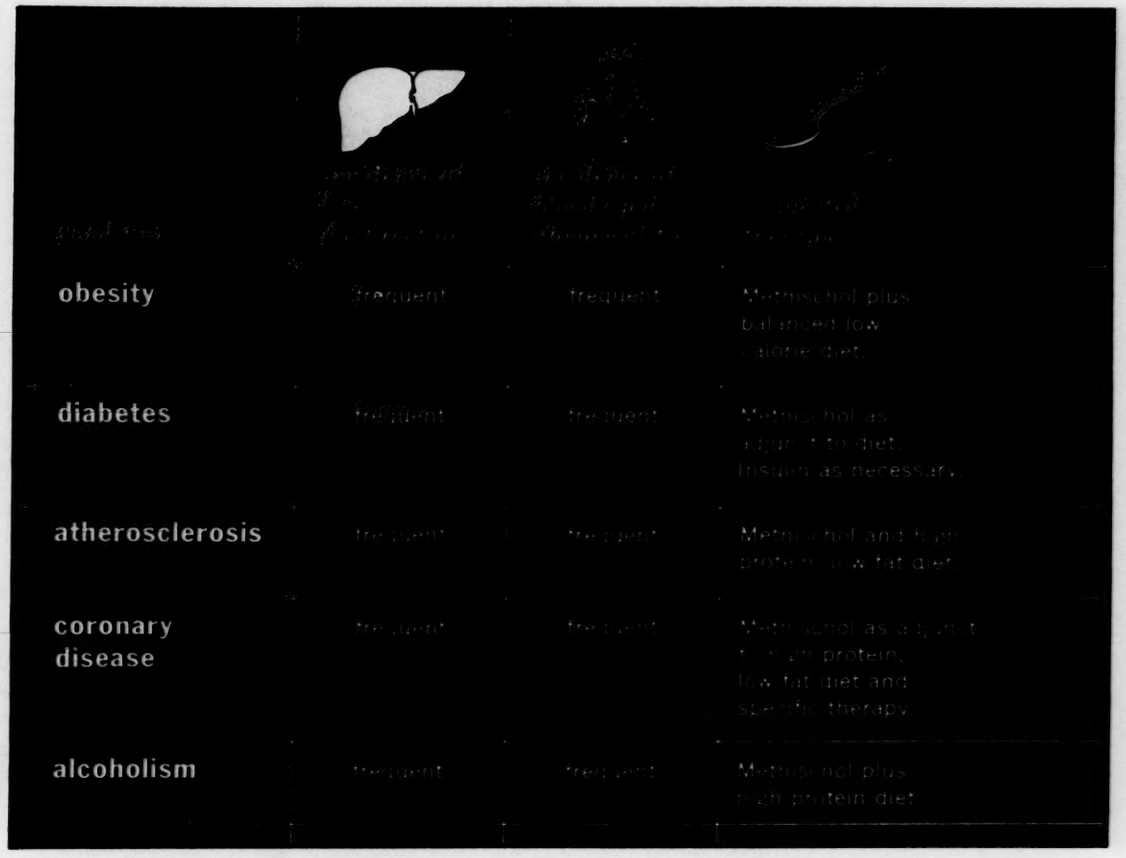
Erythromycin, Abbott
Crystalline



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the complete lipotropic therapy

... because it provides vitamin B_{12} and liver fractions in addition to choline, methionine and inositol.

... helps normalize liver function, increase phospholipid turnover, reduce fatty deposits, and stimulate regeneration of new liver cells...

... helps reduce elevated cholesterol levels and chylomicron ratios towards the normal, and aids in achieving normal fat metabolism.

now— higher B_{12}

the suggested daily therapeutic dose of 9 capsules or 3 tablespoonfuls of Methischol provides:

Choline Dihydrogen Citrate*	2.5 Gm.
dl, Methionine	1.0 Gm.
Inositol	0.75 Gm.
Vitamin B_{12}	18 mcg.
Liver Concentrate and Desiccated Liver**	0.78 Gm.

*Present in syrup as 1.15 Gm. Choline Chloride
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every patient with essential hypertension is a candidate for RAUDIXIN treatment

Because of its safety, RAUDIXIN is the drug to use first:

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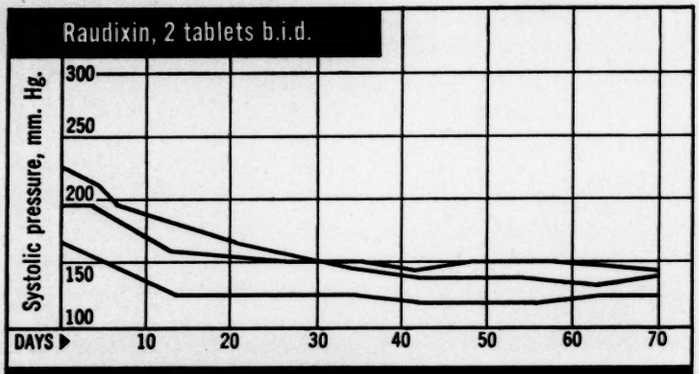
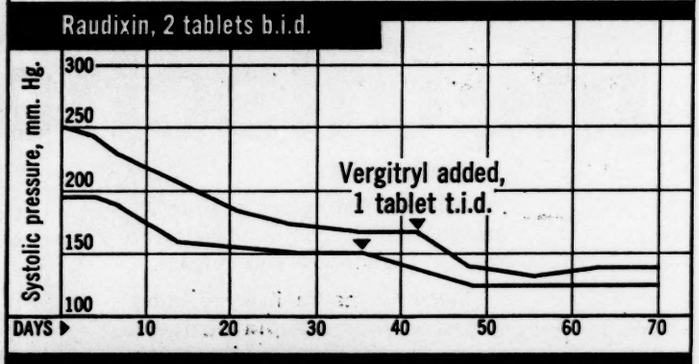
Raudixin controls most cases of mild to moderate hypertension, and some severe cases.



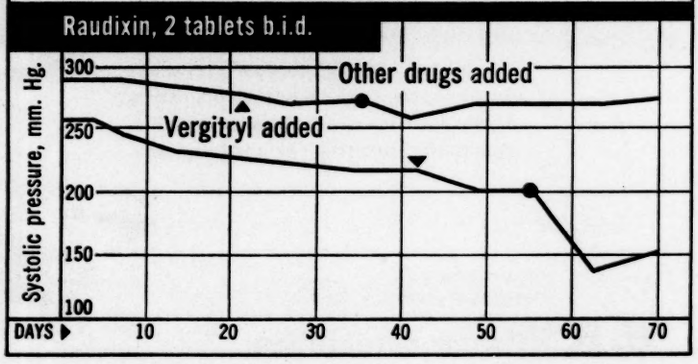
step 2

If blood pressure is not adequately controlled in four to eight weeks, Vergitryl (veratrum) may be added to Raudixin. This brings many of the remaining patients under control. Raudixin tends to delay tolerance to Veratrum, and makes smaller dosage possible.



step 3

For the few patients resistant to this combined regimen, a more potent drug may be added, for example, Bistrium (hexamethonium). The most potent drugs, which are potentially dangerous, are thus used only as a last resort in the most refractory cases.



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Squibb rauwolfia

50 mg. tablets containing the whole powdered root of Rauwolfia serpentina
Bottles of 100 and 1000

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It is universally acknowledged that the only effective means of weight reduction is restriction of caloric intake. Furthermore, it is acknowledged that no single food can be branded as fattening, that the solution to the problem is sensible limitation of the amounts of all foods eaten.

That enriched bread has a place in the modern reducing diet is evidenced by its inclusion in many weight reduction programs recommended by authorities in the fields of metabolism and internal medicine. Such a diet has recently been included in a pamphlet published by one of the nationwide organizations concerned with national health and the increasing problem of obesity.

This diet, a conventional reducing diet providing 1,200 to 1,400 calories per day, allows a balanced variety of basic foods including bread. Note the sample menu.

Enriched bread is far more than just a carbohydrate food, as is often the mistaken concept. Moreover, in itself, it is not a "fattening food," since only the calorically excessive diet can induce increase in body weight. Three slices of enriched bread provide only 189 calories, yet this amount makes a worthwhile contribution of biologically applicable protein, B group vitamins, and valuable minerals including iron and calcium. Of even greater importance to the person dieting is the gustatory attractiveness which bread lends to the meal.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

BREAKFAST
4 ounces tomato juice
1 boiled egg — 1 slice of toast
1 teaspoon butter — Coffee with milk

LUNCH
Liverwurst sandwich
(1 ounce meat, mustard, lettuce)
Celery — Small bunch grapes
1 cup of milk

DINNER
Roast chicken (3 slices, or 3 ounces)
Broccoli — 1 teaspoon butter
Asparagus — Fresh fruit cup
Tomato-cucumber salad, vinegar — Coffee or tea with milk

BEDTIME
Orange or ½ banana — ½ cup milk

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Each Phenergan expectorant troche with codeine contains:

Codeine Phosphate (⅛ gr.)	8 mg.
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Potassium Guaiacolsulfonate	162 mg.

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same formula, with the exception of codeine

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†Editorial, J. Allergy 23: 279-280, 1952.

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Announcing

℞ Rauwiloid + Hexamethonium

for the treatment of severe, intractable hypertension

- Ganglionic blockade made safer through the tranquilizing effect of Rauwiloid...
- Rauwiloid works slowly, takes time to build up. By the time hexamethonium dosage has been determined, Rauwiloid effect will have been established.
- Full hypotensive effect of hexamethonium from greatly reduced dosage (up to one-half less) because of apparently synergistic action with Rauwiloid...
- Side reactions to hexamethonium greatly reduced—in incidence as well as severity—because of lower dosage...
- Combination renders hexamethonium therapy by mouth easier to manage—a distinct advantage when severity and progression of disease demand the most potent agent available.

The inherent dangers of hexamethonium (though greatly reduced because of lower dosage required) call for the same caution, the same diligent supervision, the same careful instruction of the patient, which hexamethonium always demands.

Though the mild hypotensive effect of Rauwiloid is realized slowly, it does not impede the speedy action of hexamethonium.

Associated symptoms of severe hypertension rapidly yield to the Rauwiloid component; tachycardia is relieved by mild bradycardic influence, and gentle sedation changes the usually present anxiety to a feeling of tranquility and well-being.

The concept that it may be "better medicine" to give such potent drugs as hexamethonium individually, and not in combination, does not apply here. Unfortunate mistakes in dosage taken by the patient are less apt to occur when only one tablet-medication has to be taken.

Only the contained hexamethonium need be considered for dosage purposes. Increasing the dosage of Rauwiloid beyond the minimum effective dose will neither lead to excessive hypotensive, bradycardic, or sedative effects, nor produce side actions.

Evidence indicates hexamethonium dosage should be raised slowly. Here is a safe rate of build-up—a uniform, slow, safe rate—with this combination:

Initiate therapy with ½ tablet (each scored tablet contains Rauwiloid 1 mg. and hexamethonium 250 mg.) q.i.d., not less than 4 hours apart, preferably before meals and on retiring. After two weeks, if needed, dosage may be increased by one tablet per day, but not oftener than twice weekly.

Write today for your copy of the new brochure "Rauwiloid+Hexamethonium in the Treatment of Severe, Intractable Hypertension"; it presents a careful review of warning signs in the use of hexamethonium and of the simplification of management made possible by this combination.

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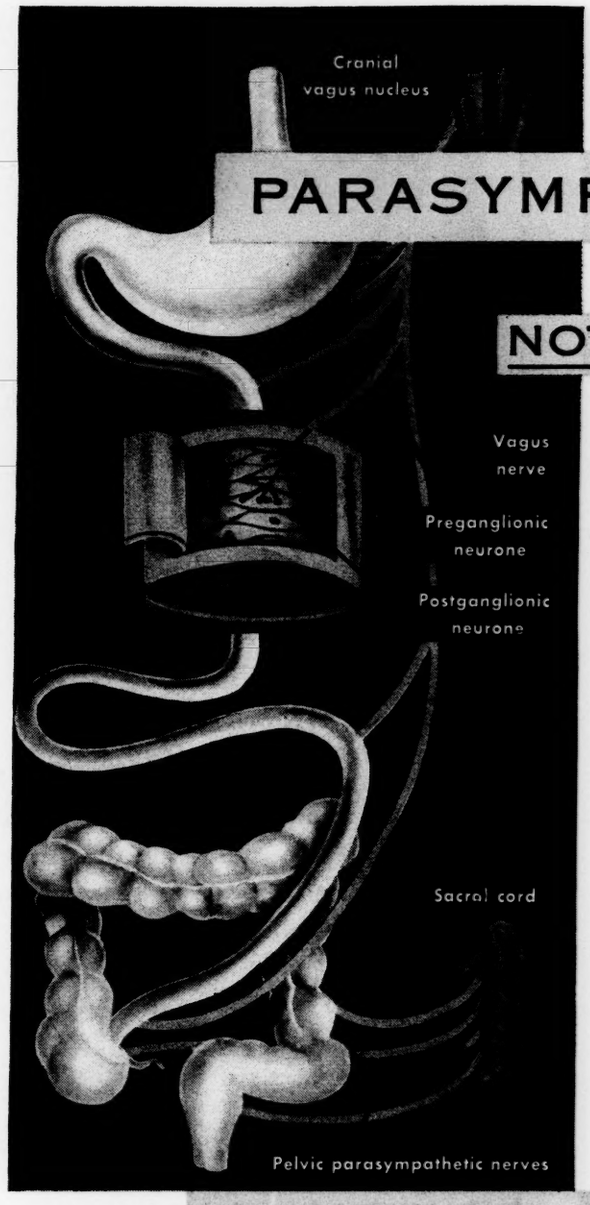

in GASTROINTESTINAL SPASM

PARASYMPATHOLYTIC . . .

NOT *parasympathomimetic*

Parasympath*olytic* (as well as spasmolytic) in all therapeutic dosages, homatropine methylbromide affords dependable relief of gastrointestinal spasm. It is thus superior to many agents which are actually parasympath*omimetic* in customary dosages and parasympath*olytic* only in high dosages attended by disturbing side effects.

In Lusyn the antispasmodic efficacy of homatropine methylbromide is reinforced by phenobarbital to allay emotional tension. Lusyn also provides the antacid-adsorbent efficiency of Alukalin.

For intestinal spasm, biliary spasm, pylorospasm, cardiospasm and irritable colon.

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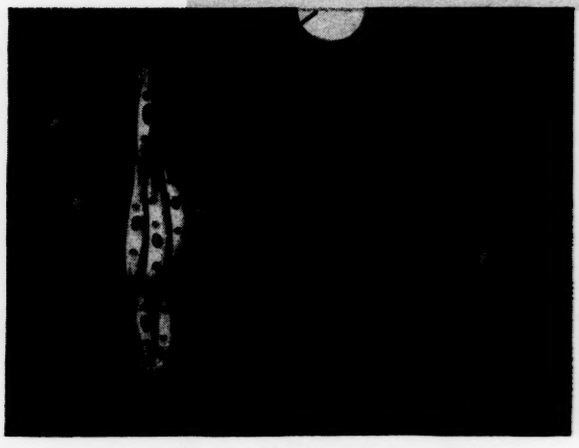

Each tablet contains:

Homatropine methylbromide..5 mg. (1/12 gr.)
(increased from 2.5 mg.)
Alukalin (activated kaolin)....300 mg. (5 gr.)
Phenobarbital .....15 mg. (¼ gr.)
(increased from 8 mg.)

Supplied: Bottles of 100, 500 and 1000 tablets.

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Full Therapeutic Dosage of Aminophylline

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- For the asthmatic patient
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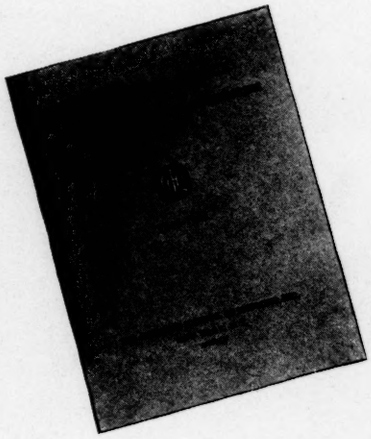
With Safety and Simplicity



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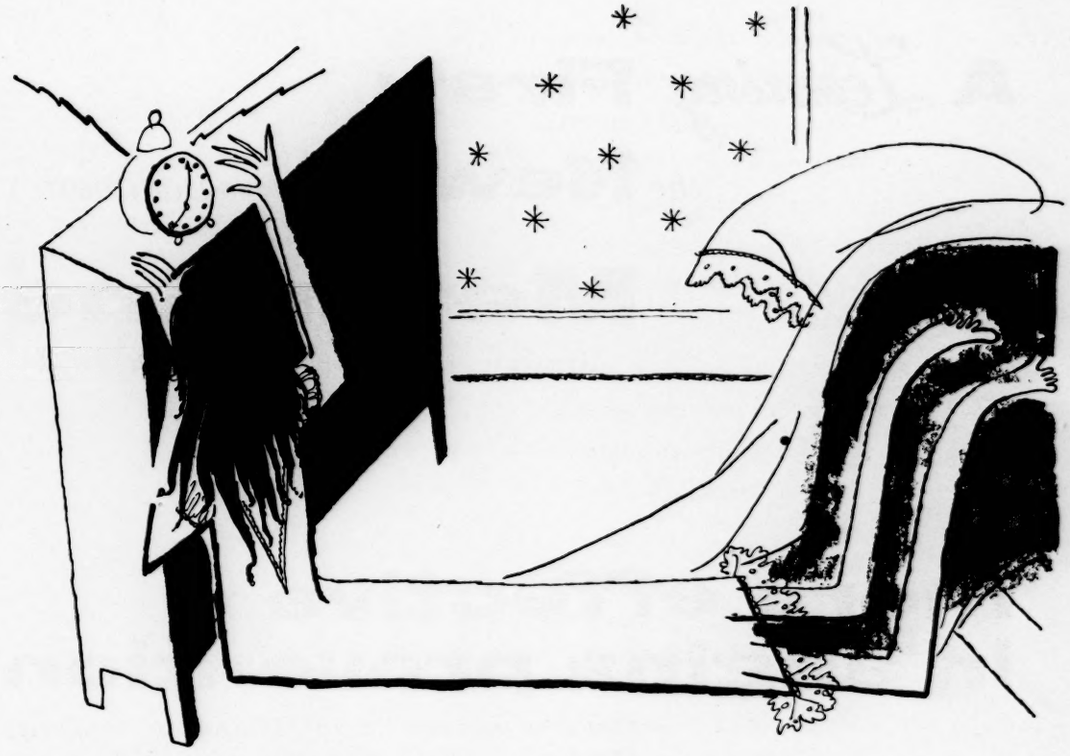

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the daily therapeutic dose, supply:

- Ferrous Sulfate..... 1.05 Gm.
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Plus these nutritional constituents:

Thiamine Mononitrate..... 6 mg.
(6 times MDR*)
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(2 times RDA†)
Ascorbic Acid .....150 mg.
(5 times MDR*)
Pyridoxine Hydrochloride.. 3 mg.
Pantothenic Acid..... 6 mg.
- Vitamin B_{12}..... 30 mcg.

Folic Acid..... 3.6 mg.
Stomach-Liver Digest.... 1.5 Gm.

*MDR—Minimum Daily Requirement
†RDA—Recommended Daily Dietary Allowance

JUST one IBEROL tablet t.i.d. assures a therapeutic dose of iron, ascorbic acid, seven B complex factors including B_{12} and folic acid, and—to conserve the hematopoietic factors—standardized stomach-liver digest. The triple-coated, compressed tablets have an outer sugar coating to mask the iron in the middle coating. No unpleasant liver odor or taste.

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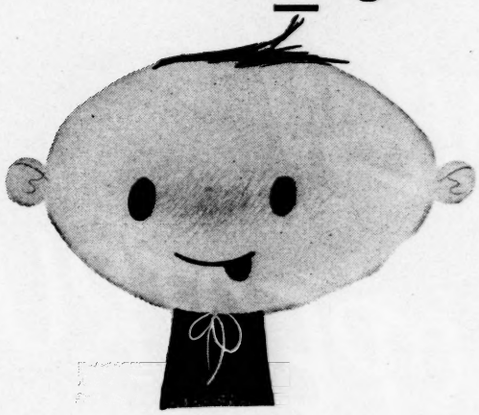

that's what physicians and patients alike call these two favorite dosage forms of Terramycin because of their unsurpassed good taste. They're nonalcoholic — a treat for patients of all ages, with their pleasant raspberry taste. And they're often the dosage forms of first choice for infants, children and adults of all ages.

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Each cc. contains 100 mg. of pure crystalline Terramycin. Supplied in 10 cc. bottles with special dropper calibrated at 25 mg. and 50 mg. May be administered directly or mixed with nonacidulated foods and liquids. Economical 1.0 gram size often provides the *total dose* required for treatment of infections of average severity in infants.

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Each 5 cc. teaspoonful contains 250 mg. of pure crystalline Terramycin. Effective against gram-positive and gram-negative bacteria, including the important coli-aerogenes group, rickettsiae, certain large viruses and protozoa.

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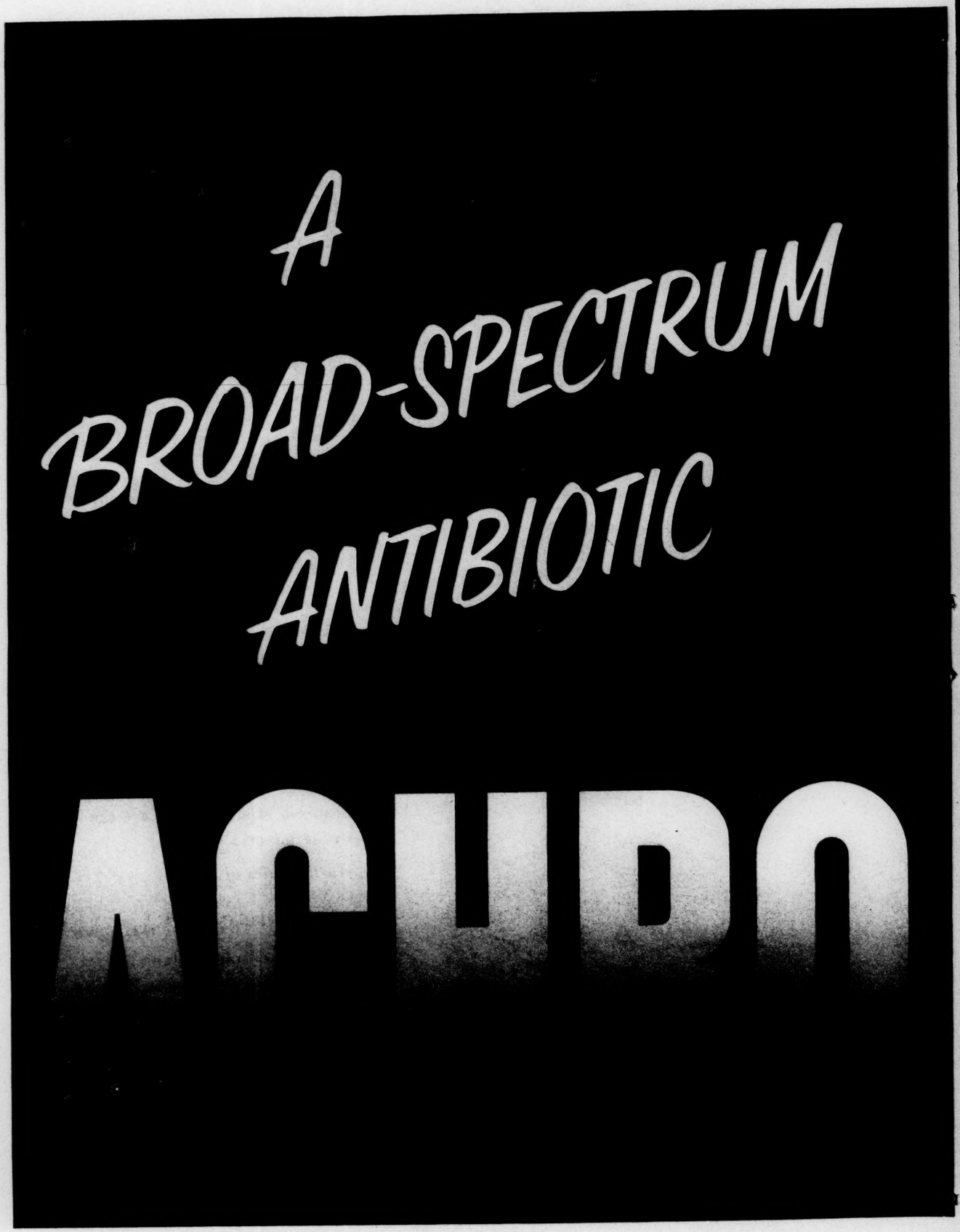
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ACHROMYCIN, a new broad-spectrum antibiotic developed by the Lederle research team, has demonstrated greater effectiveness in clinical trials with the advantages of more rapid absorption, quicker diffusion in tissue and body fluids, and increased stability resulting in prolonged high blood levels.

ACHROMYCIN exhibits a broad range of activity against beta hemolytic streptococcic infections, *E. coli* infections (including urinary tract infections, peritonitis, abscesses), meningococcic, staphylococcic, pneumococcic and gonococcic infections, otitis media and mastoiditis, acute bronchitis and bronchiolitis, actinomycosis, mixed infections and many viral and rickettsial diseases.

ACHROMYCIN is now available in 250 mg., 100 mg., and 50 mg. capsules, SPERSOIDS® 50 mg. per teaspoonful (3.0 Gm.), Intravenous 500 mg., 250 mg. and 100 mg. Other dose forms will become available as rapidly as research permits.

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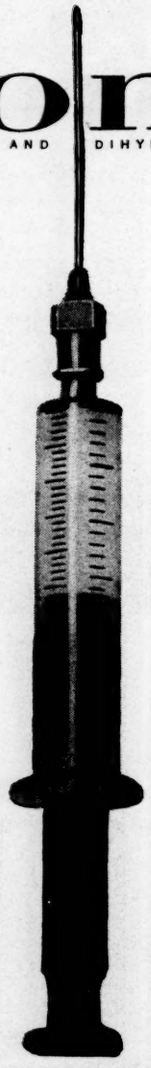
a new advance in the control of tuberculosis

Drug therapy for the management of tuberculosis continues to advance at a rapid pace. In keeping with the latest improvement—which promises a substantially lower incidence of vestibular and auditory toxicity—Pfizer has made available a new combination of streptomycin and dihydrostreptomycin—

Combistrep*

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN COMBINATION



Recent clinical studies[1] have shown that such a combination, one-half streptomycin and one-half dihydrostreptomycin, gave rise to a significant reduction in neurotoxic side effects as compared to equivalent dosage of either drug used alone, even though administered over the prolonged treatment periods required for the control of tuberculosis.

Combistrep offers these benefits to the tuberculous patient with the further assurance that its purity is of the same high standard typical of all Pfizer pharmaceuticals.

1. Heck, W. E.: Reduced Ototoxicity by Combined Streptomycin-Dihydrostreptomycin Treatment of Tuberculosis, Scientific Exhibit 317, 102nd Annual Meeting A.M.A., New York, June 1-5, 1953.

Available in vials of 1 Gm. and 5 Gm., dry powder for preparation of solutions for intramuscular injection.

also,

Streptomycin Sulfate—dry powder and solution

Dihydrostreptomycin Sulfate—dry powder and solution

Streptohydrazid*—a crystalline compound combining streptomycin and isoniazid

Cotinazin®—brand of isoniazid

Viocin* Sulfate—brand of viomycin, for resistant cases of tuberculosis

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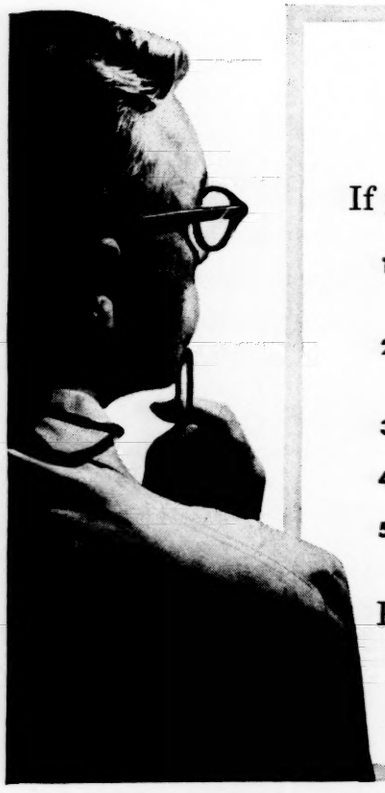

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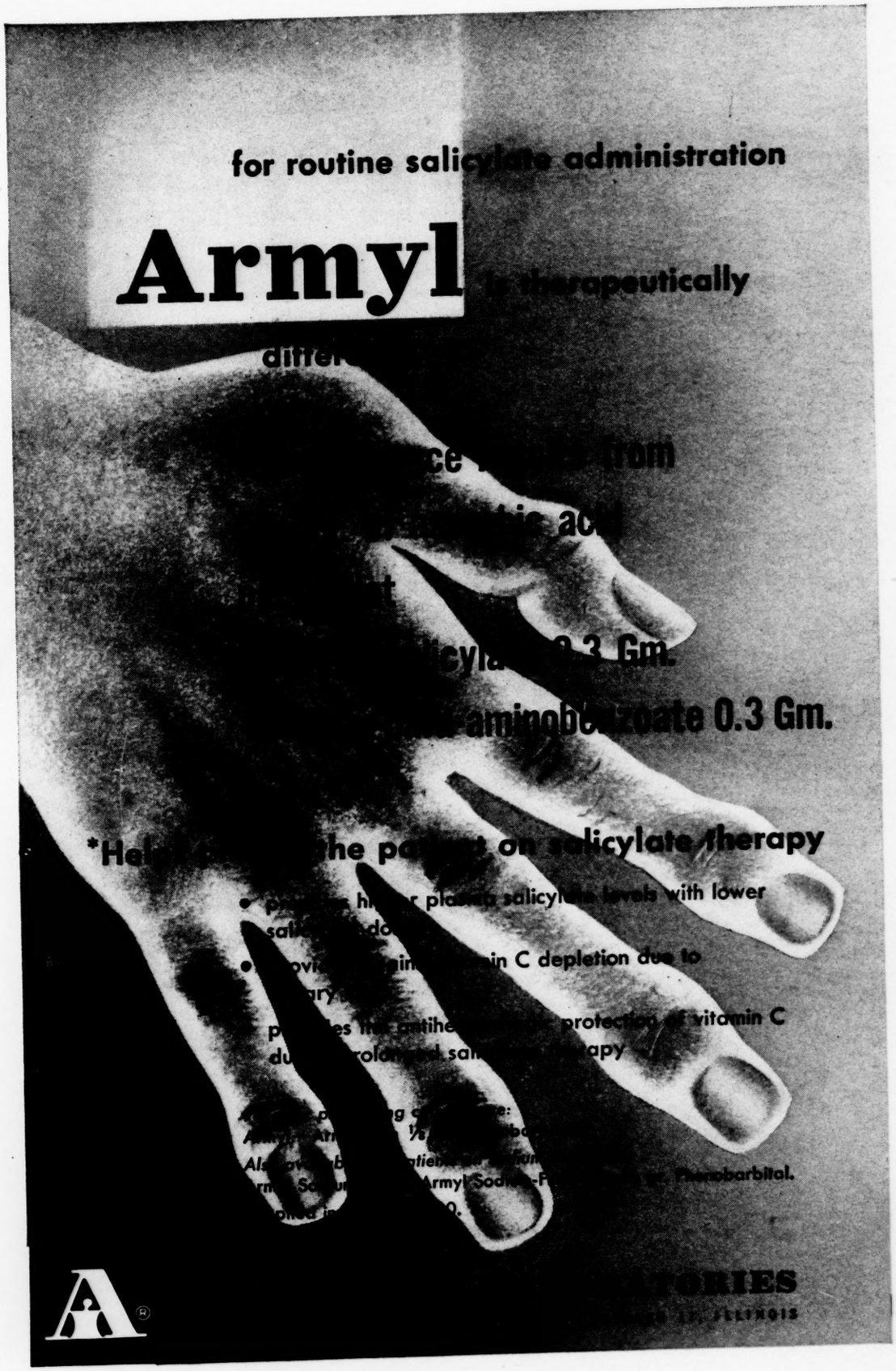
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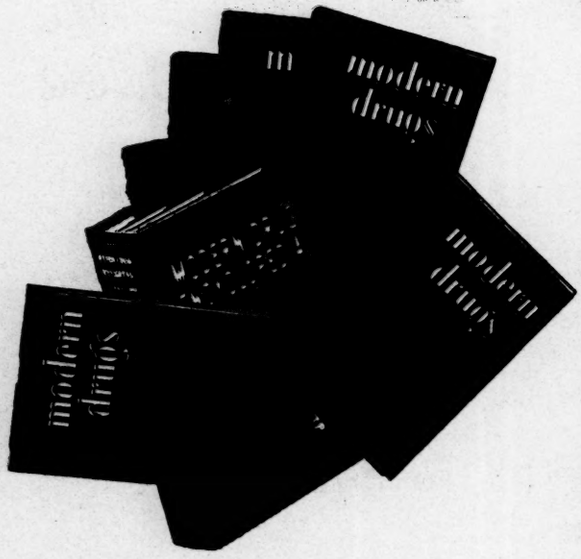

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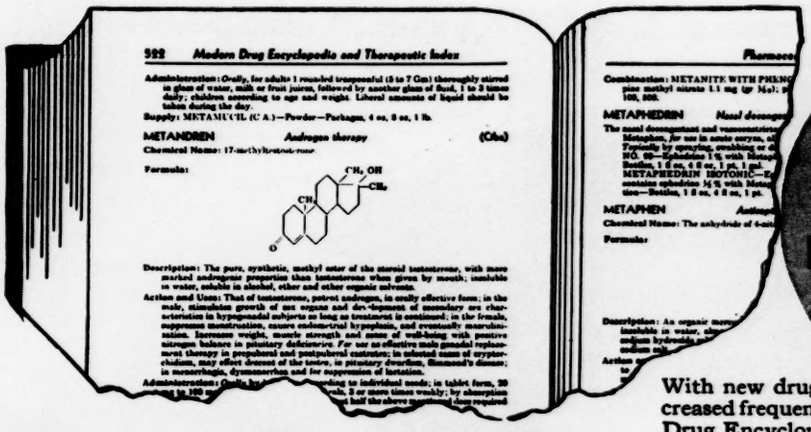
522 Modern Drug Encyclopedia and Therapeutic Index

Administration: Orally, for adults: 1 rounded teaspoonful (5 to 7 Gm) thoroughly stirred in glass of water, milk or fruit juices, followed by another glass of fluid, 1 to 3 times daily; children according to age and weight. Liberal amounts of liquid should be taken during the day.

Supply: METAMUCIL (C. A.)—Powder—Packages, 4 oz, 8 oz, 1 lb.

METANDREN Androgen therapy (Ciba)

Chemical Name: 17-methyltestosterone

Formula:

Description: The pure, synthetic, methyl ester of the steroid testosterone, with more marked androgenic properties than testosterone when given by mouth; insoluble in water, soluble in alcohol, ether and other organic solvents.

Action and Uses: That of testosterone, potent androgen, is orally effective form; in the male, stimulates growth of sex organs and development of secondary sex characteristics in hypogonadal subjects as long as treatment is continued; in the female, suppresses menstruation, causes endometrial hypoplasia, and eventually masculinization. Increases weight, muscle strength and sense of well-being with positive nitrogen balance in pituitary dwarfism. For use as effective male gonadal replacement therapy in prepubertal and postpubertal castration; in selected cases of cryptorchidism, may effect descent of the testes; in pituitary dwarfism, Simmond's disease; in menorrhagia, dysmenorrhea and for suppression of lactation.

Administration: Orally, by ... according to individual needs; in tablet form, 30 ... 2 or more times weekly; by absorption ... half the above ... than required

Pharmaco...

Combination: METANITE WITH PHEN... pine methyl nitrate 1.1 mg (as Na); ... 100, 500.

METAPHEDRIN Nasal decongest...

The nasal decongestant and vasoconstrictor ... Metaphen, for use in acute coryza, ... Topically by spraying, swabbing or ... 1%. Ophthalmic 1% with Methyl ... Benzin, 1 fl oz, 4 fl oz, 1 pt, 1 gal. METAPHEDRIN HYPOTONIC—Ea... contains ephedrine ½% with Methyl... tion—Benzin, 1 fl oz, 4 fl oz, 1 pt.

METAPHEN Antibac...

Chemical Name: The anhydride of 4-nit...

Formula:

Description: An organic mercu... insoluble in water, ... sodium hydroxide, ... sodium chl...

Action ... to ...

Encyclopedia INDEX

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pletely rewritten, the new 5th Edition of THE MODERN DRUG ENCYCLOPEDIA lists nearly 4,000 ethical drugs (including 1,500 brand new listings) of 175 manufacturers. Each listing includes latest composition, action, use, supply, dosage, caution and contra-indication of the drug. Here is data that you, too, will find indispensable for saving time, without sacrifice of an authoritative source.

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* AUDIENCE ANALYSTS, Phila., Pa.

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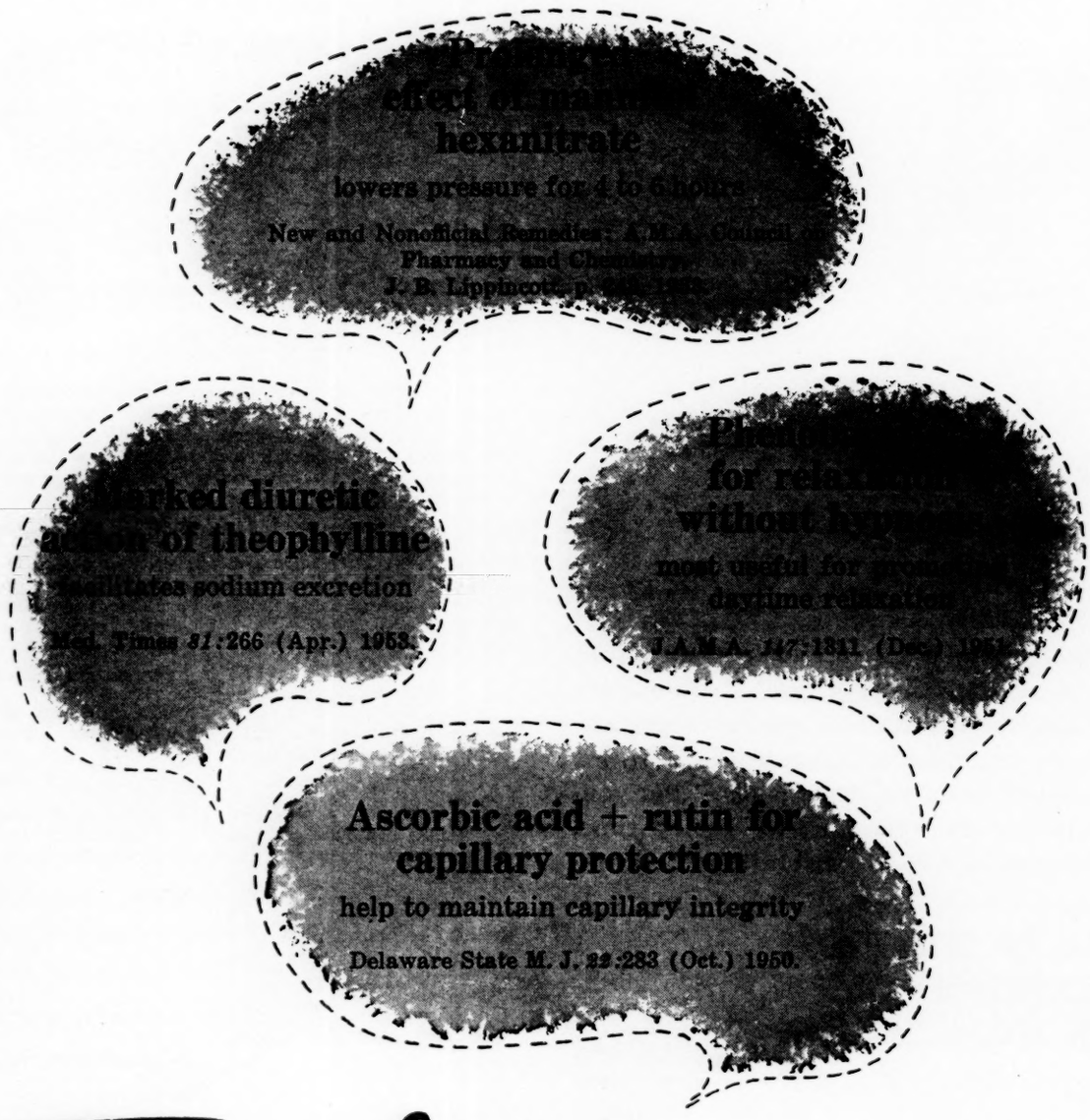
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lowers pressure for 4 to 6 hours
New and Nonofficial Remedies: A.M.A. Council on Pharmacy and Chemistry
J. B. Lippincott, p.
marked diuretic
of theophylline
facilitates sodium excretion
Med. Times 81:266 (Apr.) 1953.
without hypo
most useful for
daytime relaxation
J.A.M.A. 147:1311 (Dec.) 1951.
Ascorbic acid + rutin for
capillary protection
help to maintain capillary integrity
Delaware State M. J. 22:233 (Oct.) 1950.

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BRINGS THE PRESSURE DOWN SLOWLY **SAFELY**

Complete Medication for the Hypertensive

Each Semhyten Capsule contains:		Phenobarbital	¼ gr. (15 mg.)
Mannitol Hexanitrate	½ gr. (30 mg.)	Rutin	10 mg.
Theophylline	1½ gr. (0.1 Gm.)	Ascorbic Acid	15 mg.

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oral
estrogen-progesterone
effective in
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Cyclogesterin
TRADEMARK, REG. U. S. PAT. OFF.
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Each scored tablet contains:

Estrogenic Substances* .. 1 mg.
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Progesterone .....30 mg.

**Naturally-occurring equine estrogens (consisting primarily of estrone, with small amounts of equilin and equilenin, and possible traces of estradiol) physiologically equivalent to 1 mg. of estrone.*

Available in bottles of 15 tablets.

The Upjohn Company, Kalamazoo, Michigan

Meat...

and the Correction of Negative Nitrogen Balance

Many factors can lead to negative nitrogen balance—surgery, trauma, burns, infection, anorexia, vomiting, and diarrhea. Prompt correction of negative nitrogen balance is imperative because, as long as a nitrogen deficit exists, recovery is retarded, wound healing is slowed, blood regeneration is impeded, antibody production is reduced, weight is lost, and strength is not regained.

Yet all too frequently patients are permitted to develop—or adequate measures are not taken to correct—a negative nitrogen balance. It has been pointed out that a frequent cause for this complication is failure to recognize the increased protein needs associated with metabolic stress, with resultant failure to adjust the protein content of the diet accordingly.*

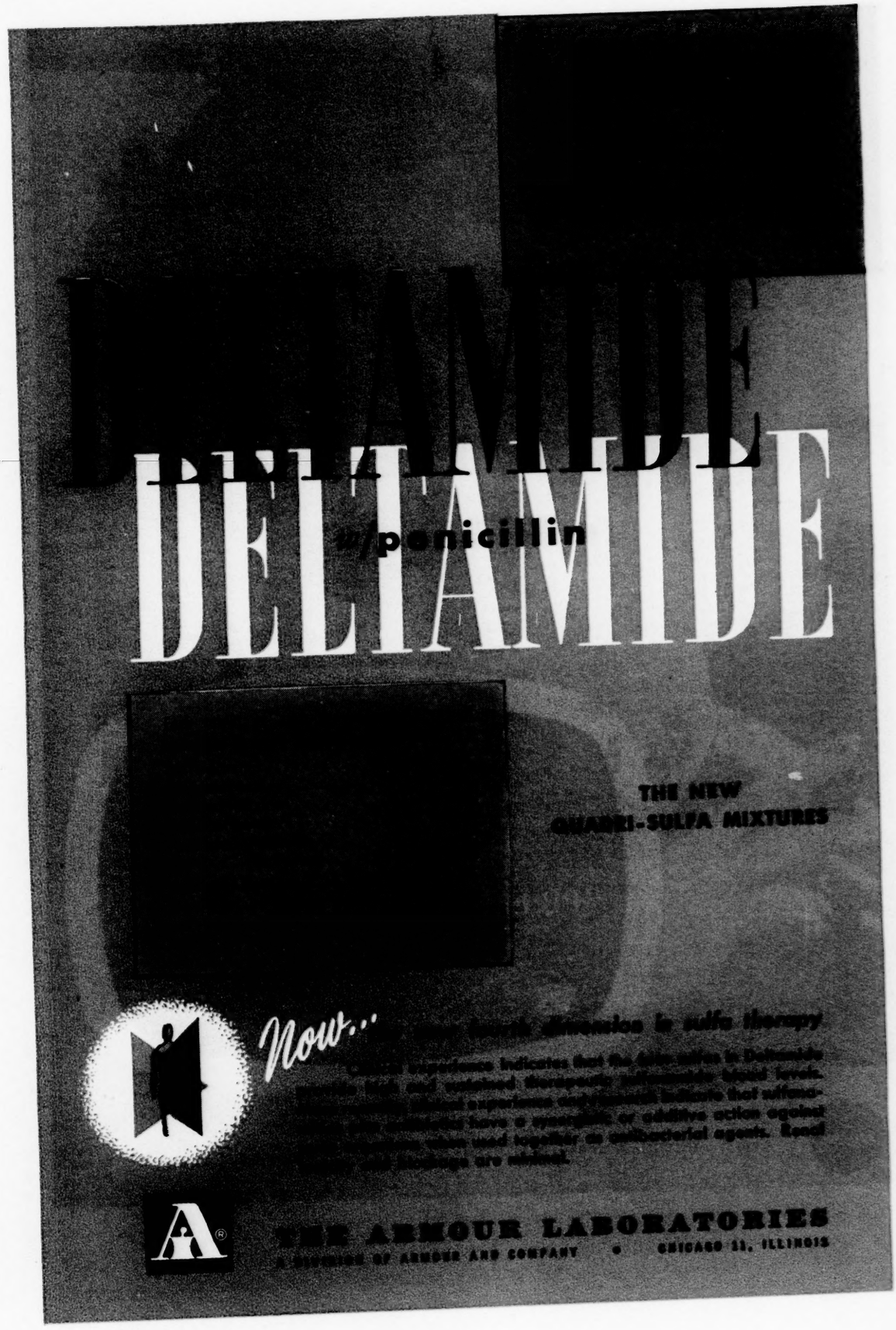
Meat in generous amounts can go far in overcoming negative nitrogen balance, regardless of cause. In surgery, the present concept of early postoperative alimentation makes possible prompt adjustment of the diet to provide the biologically complete proteins so generously supplied by meat. Furthermore, since meat can be prepared in an almost endless variety of appetizing ways, its inclusion in the diet aids in reawakening the appetite when anorexia has developed. Meat also supplies significant amounts of B vitamins and essential minerals which are also required in larger amounts during periods of stress.

---

*Pollack, H., and Halpern, S. L., in collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board: Therapeutic Nutrition, Publication 234, National Academy of Sciences —National Research Council, 1952.

The Seal of Acceptance denotes that the nutritional statements regarding meat made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute
Main Office, Chicago...Members Throughout the United States


DELTAMIDE
DELTAMIDE
w/penicillin
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THE NEW
QUADRI-SULFA MIXTURES
Now...
THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY
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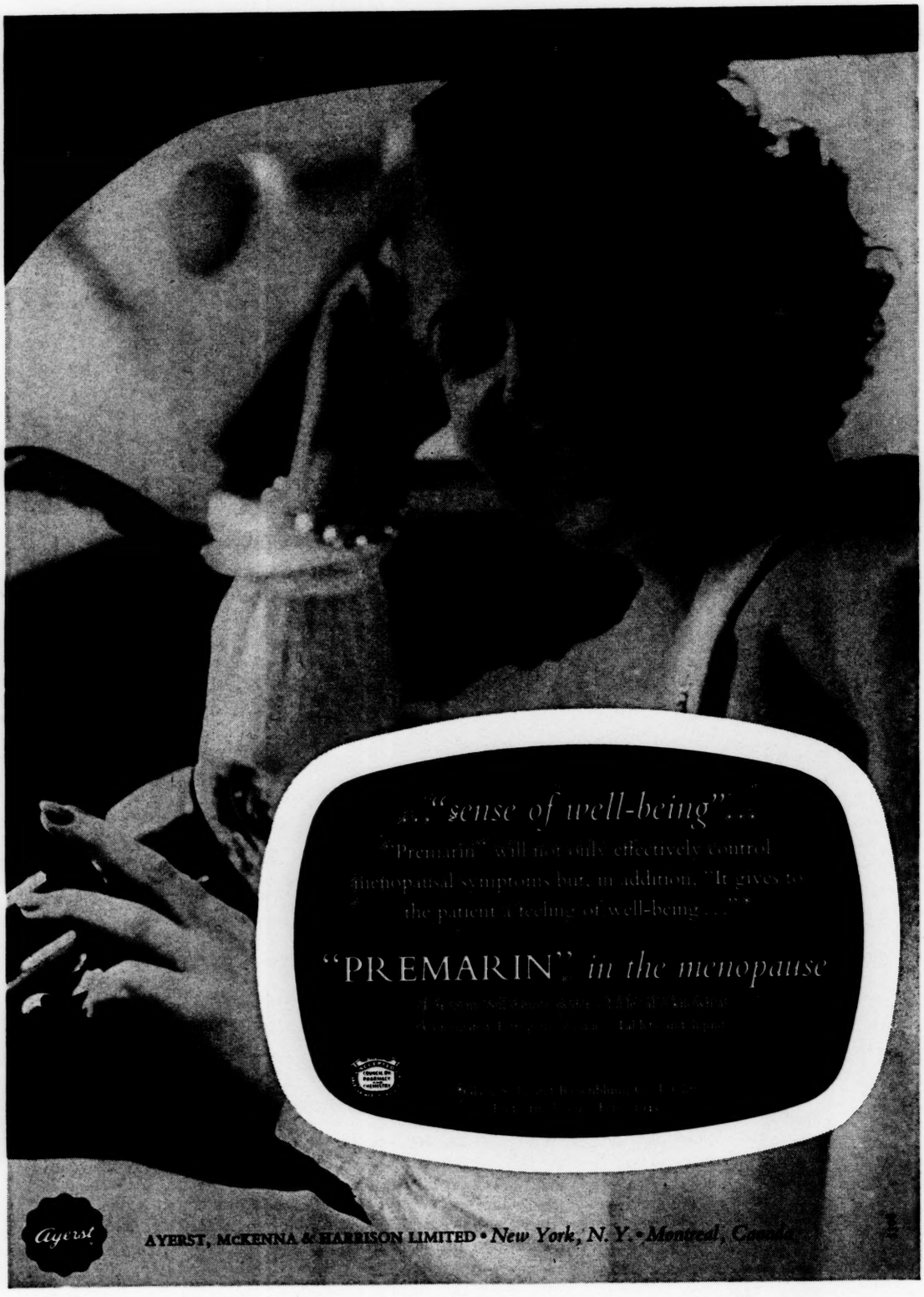
...“sense of well-being”...
“Premarin” will not only effectively control
menopausal symptoms but, in addition, “It gives to
the patient a feeling of well-being...”*
“PREMARIN” in the menopause
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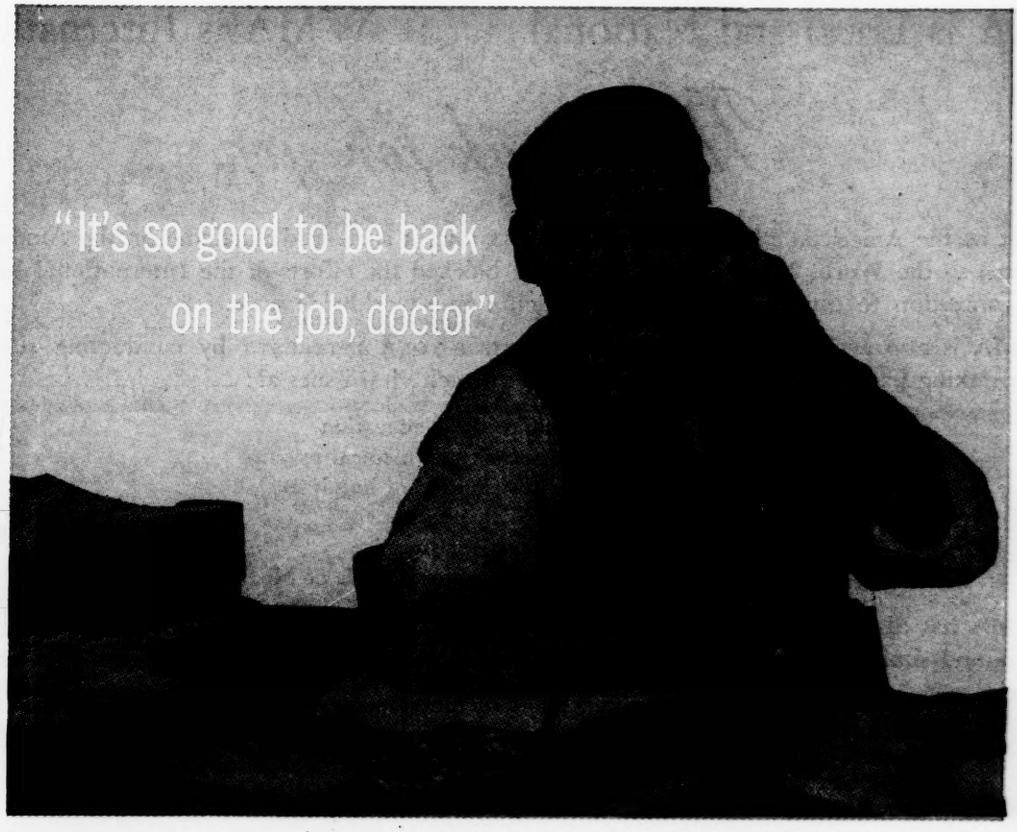
AYERST, McKENNA & HARRISON LIMITED • New York, N.Y. • Montreal, Canada

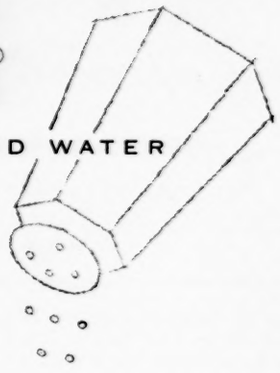


TABLET

NEOHYDRIN®

BRAND OF CHLORMERODRIN

NORMAL OUTPUT OF SODIUM AND WATER



PRESCRIBE NEOHYDRIN whenever there is retention of sodium and water except in acute nephritis and intractable oliguric states. You can balance the output of salt and water against a more physiologic intake by individualizing dosage. From one to six tablets a day, as needed.

PRESCRIBE NEOHYDRIN in bottles of 50 tablets.
There are 18.3 mg. of 3-chloromercuri-2-methoxy-propylurea in each tablet.

Leadership in diuretic research
Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

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Just as the American Medical Association has fought socialized medicine on the American scene, so the World Medical Association has blocked the efforts of the International Labor Organization to introduce socialized medicine on a worldwide scale.

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A safe tranquilizer-antihypertensive

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A pure crystalline alkaloid of Rauwolfia serpentina

Serpasil, *a pure, crystalline, single alkaloid of* Rauwolfia serpentina, *produces* mild, gradual, sustained *lowering of blood pressure without undesired effects from unknown alkaloids of the whole root. Other advantages:*

- *Effective alone or in combination with other antihypertensive agents.*
- *Uniform potency.*
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Virtually every hypertensive patient may be treated with **Serpasil** *therapy. Prescribe this* safer *tranquilizer-antihypertensive now. Available at all prescription pharmacies.*

Serpasil *Tablets, 0.25 mg.–0.1 mg. Bottles of 100.*

Ciba *Summit, New Jersey*

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"THIOSULFIL"®

brand of sulfamethylthiadiazole

The safest and most effective sulfonamide yet presented for urinary tract infections

provides these advantages...

- **Potent bacteriostatic activity**
- **Rapid transport to site of infection for early and effective urinary concentration**
- **Rapid renal clearance**
- **Minimum toxicity**
- **Minimum risk of sensitization**
- **No alkalinization required**
- **No forcing of fluids needed**

GREATER SOLUBILITY + LOWER ACETYLATION = GREATER SAFETY

Now available in two dosage forms for greater convenience

SUSPENSION

No. 914—0.25 Gm. per 5 cc.
Bottles of 4 and 16 fluidounces

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No. 785—0.25 Gm. per tablet
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5340

Detailed literature giving complete dosage schedules is available to physicians.

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Major advance in dermatitis control:

The new direct approach to the control of dermatitides is hormonal, enlisting the antiphlogistic and antiallergic potency of compound F—foremost of the corticosteroid hormones.

The new objective is adapting corticoid therapy to simple inunction treatment, and obtaining relief in various forms of dermatitides within days —sometimes within hours.

The new attainment is Cortef Acetate Ointment, which rapidly controls edema and erythema, halts cellular infiltration, arrests pruritus in such harassing skin problems as atopic dermatitis, contact dermatitis, pruritus vulvae and ani, neurodermatitis, and seborrheic dermatitis.

Cortef*

Acetate Ointment

Supplied: *Cortef Acetate Ointment is available in 5 Gm. tubes in two strengths—2.5% concentration (25 mg. per Gm.) for initial therapy in more serious cases of dermatitis, and 1.0% concentration (10 mg. per Gm.) for milder cases and for maintenance therapy.*

Administered: *A small amount is rubbed gently into the involved area one to three times a day until definite evidence of improvement is observed. The frequency of application may then be reduced to once a day or less, depending upon the results obtained.*

*TRADEMARK FOR UPJOHN'S BRAND OF HYDROCORTISONE.

A product of Upjohn Research *for medicine... produced with care... designed for health*

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RESTFUL NIGHTS and ACTIVE DAYS

FOR YOUR PATIENT

with Bronchial Asthma, Hay Fever, Urticaria

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CAPSULES
PLAIN
(for prompt action)

TABLETS
ENTERIC-COATED
(for delayed action)

One capsule and one tablet, taken at bedtime will provide almost all patients with eight hours relief and sleep. The relief can be sustained by using the capsules during the day at 4 hour intervals as required.

Each capsule and enteric-coated tablet contains:

Theophylline Sodium Acetate .....(3 gr.) 0.2 Gms.
Ephedrine Sulfate .....(½ gr.) 30 Mg.
Phenobarbital Sodium .....(½ gr.) 30 Mg.

Capsules and tablets in half the above potency available for children and mild cases in adults.

For samples just send your Rx blank marked 13LU12

Brewer EST. 1852

BREWER & COMPANY, INC.
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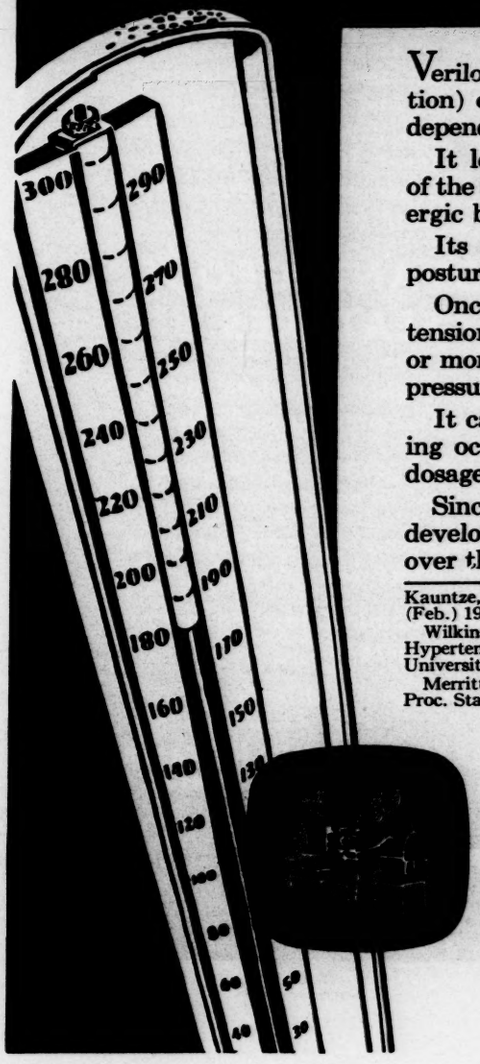
IN THE TREATMENT OF HYPERTENSION

VERILOID®

FOR THESE CARDINAL REASONS:

- around the clock action—through the day and the night—from 4 doses per day...
- no deleterious side actions—no drug-induced allergic reactions...
- great hypotensive power without the problem of developing tolerance...
- action today from today's dose.



Veriloid, the selective alkaloidal extract (alkavervir fraction) of Veratrum viride, biologically assayed in dogs, is dependably uniform in potency and action.

It lowers blood pressure promptly through mediation of the central nervous system, without ganglionic or adrenergic blockade. Not a local vasodilator.

Its administration is not fraught with the dangers of postural hypotension.

Once dosage is established, prolonged control of hypertension is possible. Even after nine months' therapy 30% or more of patients retain the induced reduction in blood pressure—a notably high percentage.

It causes no dangerous side effects. Nausea and vomiting occasioned by overdosage prove a valuable guide in dosage adjustment.

Since action is not cumulative, since tolerance does not develop, Veriloid is excellently suited "for the long pull" over the years.

Kauntze, R.: Veratrum and Its Derivatives, The Practitioner *170*:189 (Feb.) 1953.

Wilkins, R. W.: Recent Experiences with Pharmacologic Treatment of Hypertension, in Bell, E.T.: Hypertension, A Symposium, Minneapolis, University of Minnesota Press, 1951, p. 492.

Merritt, W. A.: The Treatment of Essential Hypertension with Veratrum, Proc. Staff Meet. Mayo Clin. *27*:481 (Nov. 19) 1952.

RIKER LABORATORIES, INC.

8480 Beverly Boulevard • Los Angeles 48, California

VERILOID is supplied in slow-dissolving scored tablets, in 2 and 3 mg. potencies. Initial recommended dosage, 9 mg. daily, in divided doses, not less than 4 hours apart, preferably after meals. Maintenance dose, 9 to 24 mg. per day.

VERILOID-VP provides in each scored tablet 2 mg. of Veriloid and 15 mg. of phenobarbital. Initial daily dosage, 1 or 2 tablets t.i.d. or q.i.d.

Always...

PABIRIN®

NO MATTER WHAT ELSE ARTHRITIS CALLS FOR

Regardless of other medication indicated, Pabirin is advantageous in every patient with arthritis, neuritis, myositis, gouty arthritis, or rheumatic fever. It quickly controls pain, improves joint mobility; in rheumatic fever it leads to prompt remission.

4 ADVANTAGEOUS FEATURES

- Lower dosage, higher salicylate levels, made possible by the presence of PABA.
- Sodium free, hence can be given in cardiac disease and with ACTH and cortisone.
- Better tolerated, because acetylsalicylic acid is not prone to hydrolyze in stomach.
- Guards against vitamin C loss induced by intensive salicylate therapy.

At pharmacies are supplied.

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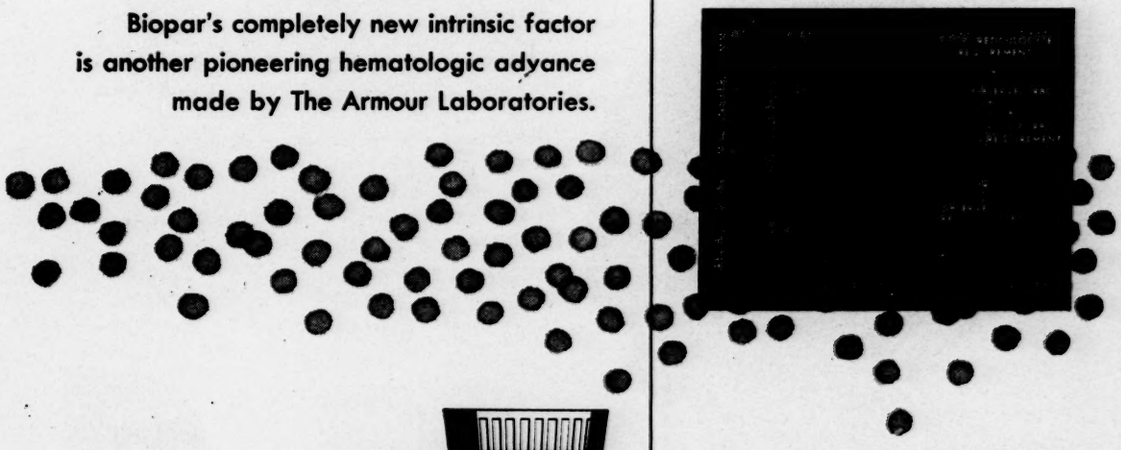
Why **BIOPAR** is an effective oral replacement for injectable vitamin B_{12}

With Biopar, effective absorption of vitamin B_{12} through the intestinal barrier is assured—even in the presence of partial or complete achlorhydria.

Absorption is assured because the intrinsic factor in Biopar performs the functions ascribed to the Intrinsic Factor of Castle.

Biopar's completely new intrinsic factor is another pioneering hematologic advance made by The Armour Laboratories.



BIOPAR®

Each Biopar tablet contains:
Crystalline Vitamin B_{12} U.S.P... 6 mcg.
Intrinsic Factor..... 30 mg.
Supplied: Bottles of 30 tablets.

Biopar produces prompt, positive reticulocyte and erythrocyte response in patients with pernicious anemia.

When you give Biopar, you can be sure that the patient is getting the full benefits of oral vitamin B_{12} therapy. Biopar is an effective method of administering vitamin B_{12} ... the patient is spared the discomfort of injection.

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physiologic relief of "morning sickness"

EMETROL®

[PHOSPHORATED CARBOHYDRATE SOLUTION]

Kinney®

In a well-controlled study, Crunden and Davis[1] recently found that EMETROL abolished or reduced the severity of pregnancy nausea in 78.8 percent of 123 patients . . . *usually within 24 hours.* In contrast, a placebo of similar taste and appearance proved moderately beneficial in only 15.6 percent of 122 controls.

EMETROL contains balanced amounts of levulose and dextrose in coacting association with orthophosphoric acid, stabilized at an optimally adjusted pH. Containing no antihistaminics, barbiturates, or narcotics, it is a safe, inexpensive, *physiologic agent* which may be given freely without stimulating or depressing the patient. Its value for a given patient can be readily appraised by the physician in a minimum of time.[1] Dosage for nausea of pregnancy — 2 tablespoonfuls taken *undiluted* immediately on arising, repeated as required if nausea recurs.

IMPORTANT: EMETROL must *not* be diluted or followed by any liquids for at least 15 minutes.

Also beneficial in vomiting associated with intestinal "flu," motion sickness, and nausea due to drug therapy or anesthesia.

SUPPLIED: Bottles of 3 fl. oz. and 16 fl. oz. through all pharmacies. *Literature and Samples on Request.*

1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.